



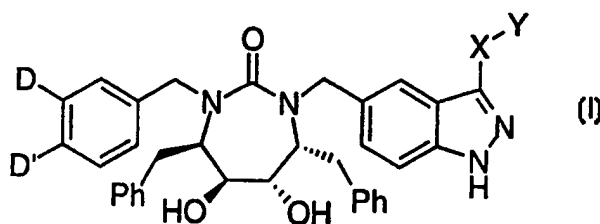
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 403/06, A61K 31/55, C07D 403/14, 401/06, 417/14, 405/14		(11) International Publication Number: WO 98/43969
A1		(43) International Publication Date: 8 October 1998 (08.10.98)
(21) International Application Number: PCT/US98/05901 (22) International Filing Date: 26 March 1998 (26.03.98) (30) Priority Data: 60/042,219 31 March 1997 (31.03.97) US (71) Applicant: DUPONT PHARMACEUTICALS COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US). (72) Inventors: RODGERS, James, David; 2 Hillside Lane, Landenberg, PA 19350 (US). JOHNSON, Barry, Laine; 404 East Christian Street, Wilmington, DE 19804 (US). WANG, Haisheng; Apartment 19, 3314 Old Capital Trail, Wilmington, DE 19808 (US). (74) Agent: VANCE, David, H.; DUPONT PHARMACEUTICALS COMPANY, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).		(81) Designated States: AU, CA, IL, JP, MX, NZ, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: INDAZOLES OF CYCLIC UREAS USEFUL AS HIV PROTEASE INHIBITORS

(57) Abstract

The present invention describes indazoles of cyclic ureas of formula (I): wherein X is a linker group and Y may be acyclic or cyclic, which are useful as inhibitors of HIV protease, and pharmaceutical compositions and diagnostic kits comprising the same. One of D and D' is NH₂ and the other selected from H, halogenes, C₁₋₆ alkoxy and C₁₋₆ alygl.



ATTORNEY DOCKET NUMBER: 10624-047-999
 SERIAL NUMBER: 09/910,950
 REFERENCE: AE

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

TITLE

Indazoles of Cyclic Ureas Useful As HIV Protease Inhibitors

5

FIELD OF THE INVENTION

This invention relates generally to indazoles of cyclic ureas which are useful as inhibitors of HIV protease, and pharmaceutical compositions and diagnostic kits comprising the same. The present invention also relates to the use of such compounds in processes for the identification of HIV protease inhibitors and for the inhibition or detection of HIV in a bodily fluid sample.

BACKGROUND OF THE INVENTION

15

Two distinct retroviruses, human immunodeficiency virus (HIV) type-1 (HIV-1) or type-2 (HIV-2), have been etiologically linked to the immunosuppressive disease, acquired immunodeficiency syndrome (AIDS). HIV seropositive individuals are initially asymptomatic but typically develop AIDS related complex (ARC) followed by AIDS. Affected individuals exhibit severe immunosuppression which predisposes them to debilitating and ultimately fatal opportunistic infections.

20

The disease AIDS is the end result of an HIV-1 or HIV-2 virus following its own complex life cycle. The virion life cycle begins with the virion attaching itself to the host human T-4 lymphocyte immune cell through the bonding of a glycoprotein on the surface of the virion's protective coat with the CD4 glycoprotein on the lymphocyte cell. Once attached, the virion sheds its glycoprotein coat, penetrates into the membrane of the host cell, and uncoats its RNA. The virion enzyme, reverse transcriptase, directs the process of transcribing the RNA into single-stranded DNA. The viral RNA is degraded and a second DNA strand is created. The now double-stranded DNA is integrated into the human cell's genes and those genes are used for virus reproduction.

30

35

At this point, RNA polymerase transcribes the integrated DNA into viral RNA. The viral RNA is translated into the

precursor *gag-pol* fusion polyprotein. The polyprotein is then cleaved by the HIV protease enzyme to yield the mature viral proteins. Thus, HIV protease is responsible for regulating a cascade of cleavage events that lead to the virus particle's maturing into a virus that is capable of full infectivity.

The typical human immune system response, killing the invading virion, is taxed because the virus infects and kills the immune system's T cells. In addition, viral reverse transcriptase, the enzyme used in making a new virion particle, is not very specific, and causes transcription mistakes that result in continually changed glycoproteins on the surface of the viral protective coat. This lack of specificity decreases the immune system's effectiveness because antibodies specifically produced against one glycoprotein may be useless against another, hence reducing the number of antibodies available to fight the virus. The virus continues to reproduce while the immune response system continues to weaken. Eventually, the HIV largely holds free reign over the body's immune system, allowing opportunistic infections to set in and without the administration of antiviral agents, immunomodulators, or both, death may result.

There are at least three critical points in the virus's life cycle which have been identified as possible targets for antiviral drugs: (1) the initial attachment of the virion to the T-4 lymphocyte or macrophage site, (2) the transcription of viral RNA to viral DNA (reverse transcriptase, RT), and (3) the processing of *gag-pol* protein by HIV protease.

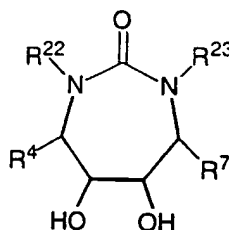
The genomes of retroviruses encode a protease that is responsible for the proteolytic processing of one or more polyprotein precursors such as the *pol* and *gag* gene products. See Wellink, *Arch. Virol.* 98 1 (1988). Retroviral proteases most commonly process the *gag* precursor into the core proteins, and also process the *pol* precursor into reverse transcriptase and retroviral protease.

The correct processing of the precursor polyproteins by the retroviral protease is necessary for the assembly of the

infectious virions. It has been shown that *in vitro* mutagenesis that produces protease-defective virus leads to the production of immature core forms which lack infectivity. See Crawford et al., *J. Virol.* 53 899 (1985); Katoh et al., *Virology* 145 280 (1985). Therefore, retroviral protease inhibition provides an attractive target for antiviral therapy. See Mitsuya, *Nature* 325 775 (1987).

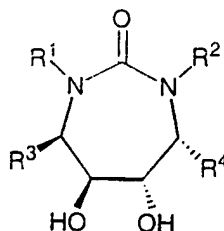
The ability to inhibit a viral protease provides a method for blocking viral replication and therefore a treatment for viral diseases, such as AIDS, that may have fewer side effects, be more efficacious, and be less prone to drug resistance when compared to current treatments. As a result, three HIV protease inhibitors, Roche's saquinavir, Abbott's ritonavir, and Merck's indinavir, are currently being marketed and a number of potential protease inhibitors are in clinical trials, e.g., Vertex's VX-478, Agouron's nelfinavir, Japan Energy's KNI-272, and Ciba-Geigy's CGP 61755.

As evidenced by the protease inhibitors presently marketed and in clinical trials, a wide variety of compounds have been studied as potential HIV protease inhibitors. One core, cyclic ureas, has received significant attention. For example, in PCT Application Number WO94/19329, Lam et al generically describe cyclic ureas of the formula:



and methods of preparing these ureas. However, Lam et al does not specifically describe the indazolyl cyclic ureas of the present invention.

In another PCT publication, WO96/29329, Jahdav et al describe cyclic ureas of the formula:



wherein R³ and R⁴ are preferably benzyl and R¹ preferably is a benzyl group having a heterocycle linked via a heteroatom
5 attached thereto. Jahdavi et al does not, though, specifically describe the indazolyl cyclic ureas of the present invention.

Even with the current success of protease inhibitors, it has been found that HIV patients can become resistant to a
10 single protease inhibitor. Thus, it is desirable to develop additional protease inhibitors to further combat HIV infection.

SUMMARY OF THE INVENTION

15 Accordingly, one object of the present invention is to provide novel protease inhibitors.

It is another object of the present invention to provide pharmaceutical compositions with protease inhibiting activity comprising a pharmaceutically acceptable carrier and a
20 therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a novel method for treating HIV infection which comprises
25 administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

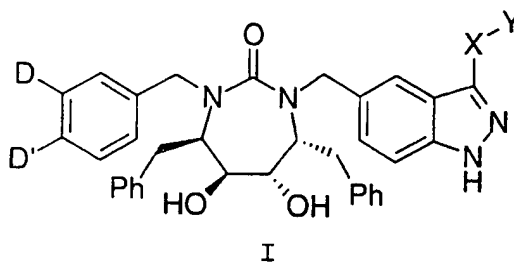
It is another object of the present invention to provide
30 a novel method for treating HIV infection which comprises administering to a host in need thereof a therapeutically effective combination of (a) one of the compounds of the present invention and (b) one or more compounds selected from

the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors.

It is another object of the present invention to provide a method of inhibiting HIV present in a body fluid sample which comprises treating the body fluid sample with an effective amount of a compound of the present invention.

It is another object of the present invention to provide a kit or container containing at least one of the compounds of the present invention in an amount effective for use as a standard or reagent in a test or assay for determining the ability of a potential pharmaceutical to inhibit HIV protease, HIV growth, or both.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula I:

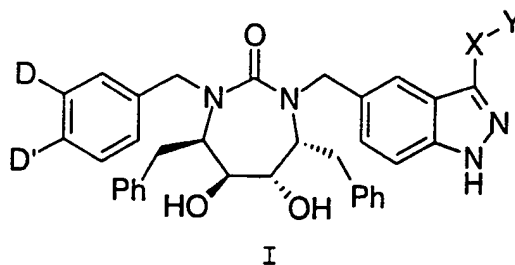


or pharmaceutically acceptable salts or prodrug forms thereof, are effective protease inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula I:

25



or a pharmaceutically acceptable salt form thereof, wherein:

one of D and D' is NH_2 and the other selected from H, halogen, C_{1-6} alkoxy, and C_{1-6} alkyl;

5 X is selected from a bond, $\text{CH}=\text{CHCH}_2$, $\text{CH}_2\text{CH}_2\text{CH}_2$, CH_2CH_2 , $\text{CH}(\text{OH})$, and CH_2 ;

10 Y is selected from OR^1 , SR^1 , NR^1R^6 , $-\text{CN}$, $-\text{OC}(\text{O})\text{NR}^1\text{R}^2$, $-\text{NR}^3\text{C}(\text{O})\text{OR}^1$, $-\text{NR}^3\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{NR}^{3a}\text{C}(\text{O})\text{R}^1$, $-\text{C}(\text{O})\text{R}^1$, $-\text{C}(\text{O})\text{OR}^1$, $-\text{C}(\text{OH})(\text{R}^2)\text{R}^1$, $-\text{SO}_2\text{R}^5$, $-\text{SO}_2\text{NR}^1\text{R}^2$, and $-(\text{CH}_2)_m\text{R}^4$;

15 R^1 is selected from H, $(\text{CH}_2)_n\text{R}^5$, C_{1-6} alkyl substituted with 0, 1, 2, or 3 R^{1a} , and C_{2-6} alkenyl substituted with 0, 1, or 2 R^{1a} ;

R^{1a} is selected from C_{1-6} alkoxy, OH, $=\text{O}$, halogen, C_{3-6} cycloalkyl, and NR^6R^{6a} ;

20 R^2 is selected from H, C_{1-4} alkyl substituted with 0, 1, or 2 R^{2b} , phenyl substituted with 0, 1, or 2 R^7 , and a 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R^7 ;

25 R^{2b} is selected from C_{1-6} alkoxy, OH, halogen, and NR^6R^{6a} ;

R^3 is selected from H and CH_3 ;

30 R^{3a} is selected from H and C_{1-3} alkyl;

R^4 is selected from a 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R^7 ;

35 R^5 is selected from a C_{3-10} carbocyclic residue substituted with 0, 1, or 2 R^7 , and a 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the

group consisting of N, O, and S substituted with 0, 1, or 2 R⁷;

R⁶ and R^{6a} are independently selected from H and C₁₋₄ alkyl;

5

R⁷ is selected from halogen, OH, =O, C₁₋₆ alkoxy, -CN, -NO₂, NR⁶R^{6a}, COR³, C₁₋₆ alkyl, CF₃, and S(O)_p(C₁₋₆ alkyl);

R⁸ is selected from H, C₁₋₆ alkyl, C₁₋₆ alkoxy, and NR⁶R^{6a};

10

m is 0, 1, 2, or 3;

n is 0, 1, or 2; and,

15 p is 0, 1, or 2.

[2] In a preferred embodiment, the present invention provides a novel compound of formula I, wherein:

20

D is NH₂;

D' is H;

25 X is CH₂; and,

Y is selected from OR¹, SR¹, NR¹R⁶, -CN, -OC(O)NR¹R², -NR³C(O)OR¹, -NR³C(O)NR¹R², -C(O)NR¹R², -NR^{3a}C(O)R¹, -C(O)R¹, -SO₂R⁵, -SO₂NR¹R², and -(CH₂)_mR⁴.

30

[3] In a more preferred embodiment, the present invention provides a novel compound of formula I, wherein:

35 Y is selected from OR¹, SR¹, -OC(O)NR¹R², -NR³C(O)OR¹, -NR³C(O)NR¹R², -C(O)NR¹R², -NR^{3a}C(O)R¹, -C(O)R¹, -C(O)OR¹, -SO₂R⁵, -SO₂NR¹R², and -(CH₂)_mR⁴.

R^1 is selected from H, $(CH_2)_nR^5$ and C_{1-5} alkyl substituted with 0, 1, 2, or 3 R^{1a} ;

5 R^2 is selected from H, C_{1-4} alkyl substituted with 0, 1, or 2 R^{2b} , phenyl substituted with 0, 1, or 2 R^7 , and a 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R^7 ; and,

10 R^5 is selected from a C_{6-10} aromatic carbocyclic residue substituted with 0, 1, or 2 R^7 , and a 5-10 membered aromatic heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R^7 .

15

[4] In an even more preferred embodiment, the present invention provides a novel compound of formula I, wherein:

20 Y is selected from OR^1 , SR^1 , $-OC(O)NR^1R^2$, $-C(O)NR^1R^2$, $-NR^3C(O)OR^1$, $-NR^3C(O)R^1$, $-C(O)R^1$, and $-(CH_2)_mR^4$.

R^1 is selected from $(CH_2)_nR^5$ and C_{1-6} alkyl;

25 R^4 is selected from a 5-10 membered aromatic heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R^7 ;

30 R^5 is selected from a C_{6-10} aromatic carbocyclic residue substituted with 0, 1, or 2 R^7 , and a 5-10 membered aromatic heterocyclic system containing from 1-2 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R^7 ;

35

R^7 is selected from halogen, OH, C_{1-6} alkoxy, $-CN$, $-NO_2$, NR^6R^{6a} , COR^8 , C_{1-6} alkyl, CF_3 , and $S(O)_2(C_{1-4} \text{ alkyl})$; and,

m is 0, 1, or 2.

[5] In a further preferred embodiment, the present invention
5 provides a novel compound of formula I, wherein:

R² is selected from H, C₁₋₄ alkyl substituted with 0, 1, or 2
R^{2b}, phenyl substituted with 0, 1, or 2 R⁷, and a 5-10
10 membered heterocyclic system containing from 1-2
heteroatoms selected from the group consisting of N, O,
and S substituted with 0, 1, or 2 R⁷; and,

R⁷ is selected from Cl, F, I, OH, C₁₋₆ alkoxy, -CN, -NO₂,
NR⁶R^{6a}, COR⁸, C₁₋₆ alkyl, CF₃, and S(O)₂(C₁₋₄ alkyl); and,
15 n is 0 or 1.

[6] In another preferred embodiment, the present invention
20 provides a novel compound of formula I, wherein:

D is NH₂;

D' is H;

25

X is CH₂; and,

Y is selected from:

30 phenylmethoxy; phenylthio; 2-benzimidazolylthio;
2-quinolinylmethoxy; 4-trifluoromethylphenoxy; 6-
quinolinoxy; 5-quinolinoxy; 4-quinolinoxy; 2-
methylphenoxy; 3-fluorophenylmethoxy; 2-
fluorophenylmethoxy; ethoxy; 7-quinolinoxy; 4-
35 methylphenylmethoxy; 4-trifluoromethylphenylmethoxy; 3-
methylphenoxy; 3-aminophenoxy; 2-aminophenoxy; 3-
methylphenylmethoxy; 3-trifluoromethylphenylmethoxy; 5-
(2-methyl)benzthiazoloxy; 5-benzthiazoloxy; n-butoxy; 4-

5 cinnolinoxy; 4-fluoro-2-aminophenoxy; methyl carbamoyl;
4-cyano-2-methoxyphenoxy; i-butyl carbamoyl; methoxy; 1-
(5-methyl)indazole; ethyl carbamoyl; N-phenyl carbamoyl;
1-pyrazole; n-propyl carbamoyl; 3,4-dimethoxyphenoxy; n-
butyl carbamoyl; i-propyl carbamoyl; t-butyl carbamoyl;
trifluoroacetamido; 2,2,2-trifluoroethyl carbamoyl; 3-
tetrahydrofuranyl carbamoyl; 1-(4-methyl)pyrazole; 1-(4-
chloro)pyrazole; 1-(4-bromo)pyrazole; 2-pyridinyl
carboxamido; phenyl carboxamido; 1-(4-amino)pyrazole; 1-
10 (3-trifluoromethyl)pyrazole; 1-(3,5-dimethoxy)pyrazole;
1-(3-amino)pyrazole; 2-furanyl carboxamido; 2-thiophenyl
carboxamido; 1-(4-iodo)pyrazole; 1-(4-nitro)pyrazole; 1-
(3-nitro)pyrazole; t-butyl carboxamido; 3-
trifluoromethylphenyl carboxamido; 3-methoxyphenyl
15 carboxamido; 4-methoxyphenyl carboxamido; 2-quinolinyl
carboxamido; 2-pyrazinyl carboxamido; 1-i-quinolinyl
carboxamido; 2-methoxyphenyl carboxamido; 1-(4-
carboethoxy)pyrazole; 2-fluorophenyl carboxamido;
3-fluoro-5-trifluoromethylphenoxy; 4-fluorophenyl
20 carboxamido; 8-(1,2,3,4-tetrahydro)quinolinyl
carboxamido; 2-(6-methyl)pyridinyl carboxamido; 2-
aminophenyl carboxamido; 3-aminophenyl carboxamido; 4-
aminophenyl carboxamido; 2,6-difluorophenyl carboxamido;
1-(4-acetyl)pyrazole; 1-(4-carbomethoxy)pyrazole; 2-
25 pyridylmethoxy; 2-methyl-4-thiazolemethoxy; propoxy;
N,N-dimethylcarbamoyl; 6-methyl-2-pyridylmethoxy;
phenoxy; 2-isopropyl-4-thiazolemethoxy; 4-methylphenoxy;
4-methoxyphenoxy; 4-cyanophenoxy; 3-pyridoxy; 2-methyl-
6-benzothiazoloxo; 5-trifluoromethyl-2-pyridylmethoxy;
30 N-methylcarbamoyl; N-isopropylcarbamoyl; 2-methyl-5-
pyridoxy; 1,2,4-triazole; benzoyl; N-t-butylcarboxamido;
N,N-diethylcarboxamido; N-phenylcarboxamido;
pyrrolidinecarboxamido; 4-fluorophenoxy; 3-
fluorophenoxy; 4-fluorophenylmethoxy; 2-naphthylmethoxy;
35 2-naphthoxy; 2-fluorophenoxy; 4-chlorophenoxy;
2,4-di-fluorophenoxy; 4-(methylsulfonyl)phenoxy; 2-
fluoro-3-pyridoxy; 2-benzothiazolemethoxy; 3-
cyanophenoxy; 3,4-di-fluorophenoxy; 2-fluoro-4-

pyridylmethoxy; 6-fluoro-2-pyridylmethoxy; 5-chloro-3-pyridoxy; 3-chloro-6-pyridazoxy; 8-quinolinoxy; 6-chloro-2-pyridylmethoxy; 2-chloro-3-pyridoxy; 3-methoxyphenoxy; 2-methoxyphenoxy; 3-furanoxy; 3-acetylphenoxy; 2-thiazole; 2-benzimidazole; N-methyl-2-imidazole; 4-acetyl phenoxy; 6-cyano-2-pyridyl; 2-pyrazole; 2-benzothiazole; phenylmethyl; 2-pyridyl; 2-isoxazole; and, 2-furan;

10

In a second embodiment, the present invention provides a novel pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt form thereof.

In a third embodiment, the present invention provides a novel method for treating HIV infection which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt form thereof.

In a fourth embodiment, the present invention provides a novel method of treating HIV infection which comprises administering, in combination, to a host in need thereof a therapeutically effective amount of:

- (a) a compound of formula I; and,
- (b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors.

In another preferred embodiment, the reverse transcriptase inhibitor is a nucleoside reverse transcriptase inhibitor.

In another more preferred embodiment, the nucleoside reverse transcriptase inhibitor is selected from AZT, 3TC, ddI, ddC, and d4T and the protease inhibitor is selected from saquinavir, ritonavir, indinavir, VX-478, nelfinavir, KNI-
5 272, CGP-61755, and U-103017.

In an even more preferred embodiment, the nucleoside reverse transcriptase inhibitor is selected from AZT and 3TC
10 and the protease inhibitor is selected from saquinavir, ritonavir, and indinavir.

In a still further preferred embodiment, the nucleoside
15 reverse transcriptase inhibitor is AZT.

In another still further preferred embodiment, the
20 protease inhibitor is indinavir.

In a fifth embodiment, the present invention provides a pharmaceutical kit useful for the treatment of HIV infection, which comprises a therapeutically effective amount of:
25 (a) a compound of formula I; and,
(b) at least one compound selected from the group consisting of HIV reverse transcriptase inhibitors and HIV protease inhibitors, in one or more sterile containers.

30 In a sixth embodiment, the present invention provides a novel method of inhibiting HIV present in a body fluid sample which comprises treating the body fluid sample with an effective amount of a compound of formula I.
35

In a seventh embodiment, the present invention to provides a novel a kit or container comprising a compound of

formula I in an amount effective for use as a standard or reagent in a test or assay for determining the ability of a potential pharmaceutical to inhibit HIV protease, HIV growth, or both.

5

DEFINITIONS

As used herein, the following terms and expressions have the indicated meanings. The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6 , then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6 . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then

such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

5 As used herein, "C₁₋₆ alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, examples of which include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, 10 pentyl, and hexyl; "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like.

15 "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

As used herein, "carbocycle" or "carbocyclic residue" is 20 intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 25 cycloheptyl, adamantyl, cyclooctyl,; [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic 30 system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the 35 group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be

attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinoliziny, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, β -carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl., oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl,

pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranlyl, 5 tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 10 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazoliny, or isatinoyl. 15 Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, "HIV reverse transcriptase inhibitor" is intended to refer to both nucleoside and non-nucleoside inhibitors of HIV reverse transcriptase (RT). Examples of 20 nucleoside RT inhibitors include, but are not limited to, AZT, ddC, ddI, d4T, and 3TC. Examples of non-nucleoside RT inhibitors include, but are no limited to, viviradine (Pharmacia and Upjohn U90152S), TIBO derivatives, BI-RG-587, nevirapine, L-697,661, LY 73497, and Ro 18,893 (Roche).

25 As used herein, "HIV protease inhibitor" is intended to refer to compounds which inhibit HIV protease. Examples include, but are not limited, saquinavir (Roche, Ro31-8959), ritonavir (Abbott, ABT-538), indinavir (Merck, MK-639), VX-478 (Vertex/Glaxo Wellcome), nelfinavir (Agouron, AG-1343), 30 KNI-272 (Japan Energy), CGP-61755 (Ciba-Geigy), and U-103017 (Pharmacia and Upjohn). Additional examples include the protease inhibitors disclosed in WO93/07128, WO 94/19329, WO 94/22840, PCT Application Number US96/03426, WO96/28464, WO95/33464, and WO95/06030.

35 As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts

include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula I or other formulae or compounds of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the present invention, for example formula (I), are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein the hydroxy or amino group is bonded to any group that, when the prodrug is administered to a mammalian subject, cleaves to form a free hydroxyl or free amino, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, or benzoate derivatives of alcohol and amine functional groups in the compounds of formula I; phosphate esters, dimethylglycine esters, aminoalkylbenzyl esters, aminoalkyl esters and carboxyalkyl esters of alcohol functional groups in the compounds of formula I; and the like. Additional examples include compounds wherein the two hydroxy groups of formula I join to form an epoxide; $-OCH_2SCH_2O-$; $-OC(=O)O-$; $-OCH_2O-$; $-OC(=S)O-$; $-OC(=O)C(=O)O-$; $-OC(CH_3)_2O-$; $-OC((CH_2)_3NH_2)(CH_3)O-$; $-OC(OCH_3)(CH_2CH_2CH_3)O-$; or $-OS(=O)O-$.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Only stable compounds are contemplated by the present invention.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., $=O$) group, then 2 hydrogens on the atom are replaced.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or

an amount of the combination of compounds claimed effective to inhibit HIV infection or treat the symptoms of HIV infection in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the effect (in this case, inhibition of HIV replication) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

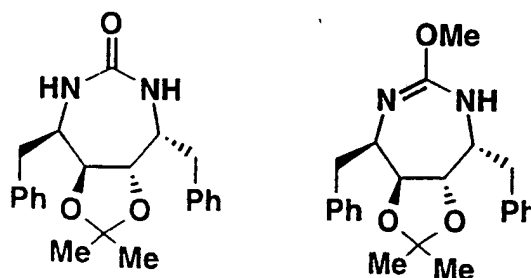
15

SYNTHESIS

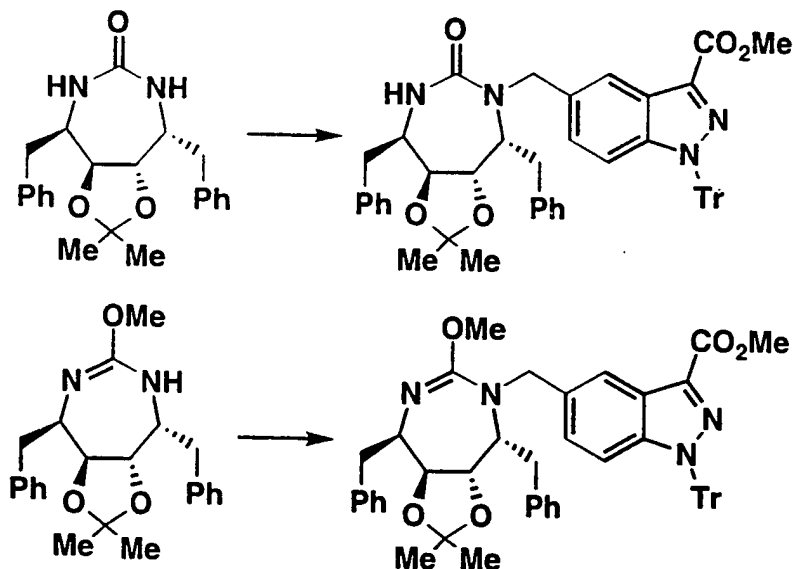
The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the

trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991). All references cited herein are hereby incorporated in their entirety herein by reference.

- 5 Two of the common starting materials useful for making compounds of the present invention are shown below.



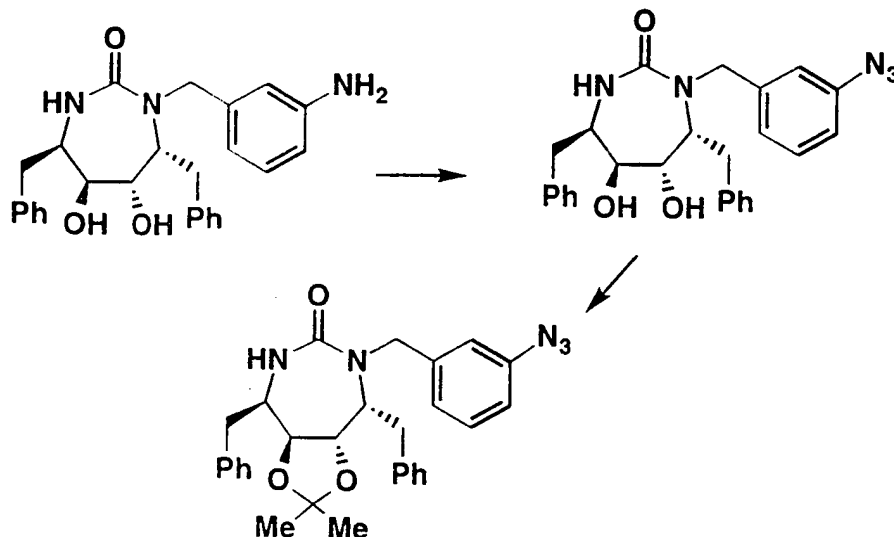
- 10 The cyclic urea can be prepared as shown in Example 6 of U.S. Patent No. 5,530,124, the contents of which are hereby incorporated by reference. The vinyl ether can be prepared as shown in Example 3 of U.S. Patent No. 5,532,357, the contents of which are hereby incorporated by reference.
- 15 One can alkylate these starting materials with an appropriately substituted indazolylmethyl group as shown below.



- 20 Descriptions of reactions of this type will be provided in the Example section. The remaining urea nitrogen can then be

alkylated with an appropriate benzyl group, e.g., m-nitrobenzylchloride. The ester group of the indazole can then be further modified to obtain the presently claimed compounds. These modifications will be described in detail in the following section.

It may be advantageous to first alkylate the cyclic urea with a benzyl group.



10

The aminobenzyl-cyclic urea can be obtained from reduction of the reaction product of a cyclic urea and m-nitrobenzylchloride. By alkylating with the benzyl group first, one can modify the benzyl substituent so that it will not be effected by subsequent modifications of the indazole ester.

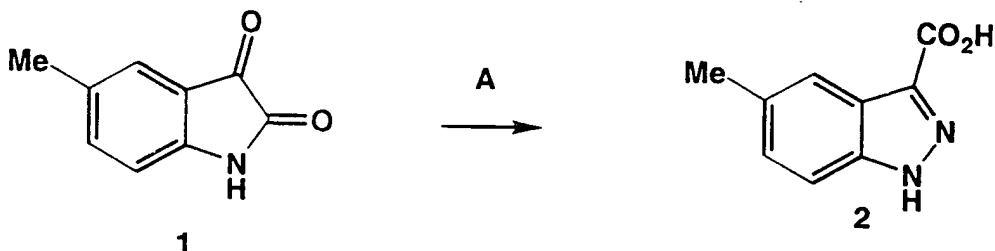
Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

Examples

Abbreviations used in the Examples are defined as follows: "°C" for degrees Celsius, "d" for doublet, "dd" for doublet of doublets, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "H" for hydrogen or hydrogens,

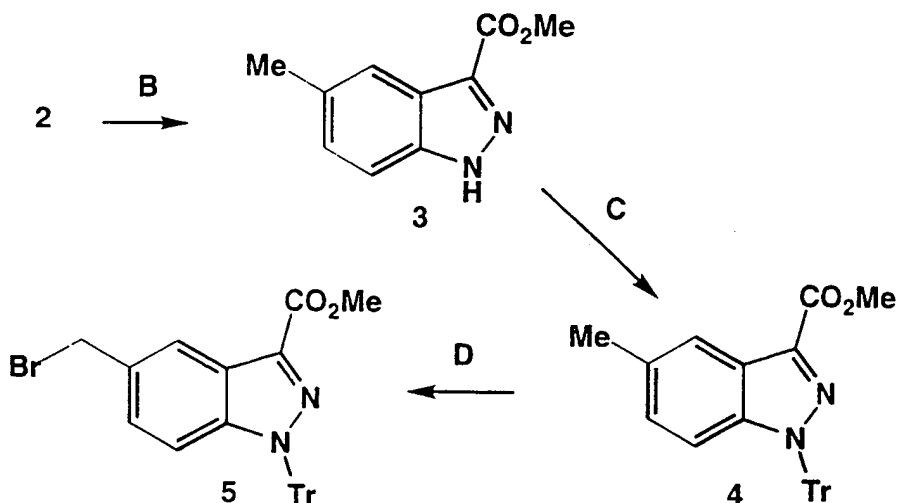
"hr" for hour or hours, "m" for multiplet, "M" for molar, "min" for minute or minutes, "MHz" for megahertz, "MS" for mass spectroscopy, "nmr" or "NMR" for nuclear magnetic resonance spectroscopy, "t" for triplet, and "TLC" for thin layer chromatography.

General. All reactions were run under a nitrogen atmosphere at room temperature and most were unoptimized. The reactions were followed by TLC. Reactions that had been run over night were done so out of convenience. Reagents were used as received. DMF, THF and acetonitrile were dried over molecular sieves. All other solvents were reagent grade. Ethanol and methanol were absolute and water was deionized. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Column chromatographies were done on flash silica gel. Exceptions to any of the conditions above are note in the text.



Method A: The 5-methylisatin (5.08 g, 31.6 mmol) was dissolved with NaOH (1.30 g, 32.5 mmol) in water (10mL). The solution was chilled to 0°C) and added to a chilled (0°C) solution of NaNO₂ (2.19 g, 31.7 mmol) in water (10 mL). The combined solution was added (5-10 min.) with stirring to a chilled (0°C) solution of concentrated H₂SO₄ (6.33 g, 64.6 mmole) in water (60 mL) using a dropping funnel with the tip below the surface of the acid. During the addition, ice was added to the reaction as needed to maintain a 0°C) operating temperature and ether was added to control foaming. The diazonium salt solution was added (15-20 min.) with stirring to a chilled (0°C) mixture of tin chloride dihydrate (17.4 g, 77.0 mmol) in concentrated H₂SO₄ (30 mL) by way of a dropping funnel with the tip below the surface of the acid. During

the addition, ice was added to the reaction as needed to maintain a 0°C operating temperature and ether was added to control foaming. After stirring for one hour, the reaction was filtered giving a golden yellow powder. The powder was dissolved in water (50 mL) by adding solid KOH until a constant pH of 8.5 was achieved. The mixture was filtered through celite with water and washed with ethyl acetate (3x30 mL). The aqueous fraction was acidified (pH 2) with concentrated HCl and the precipitate was filtered which gave 4.52 g of 2 as a yellow powder (81%): mp >350°C; mass spec. 177 (M+H).



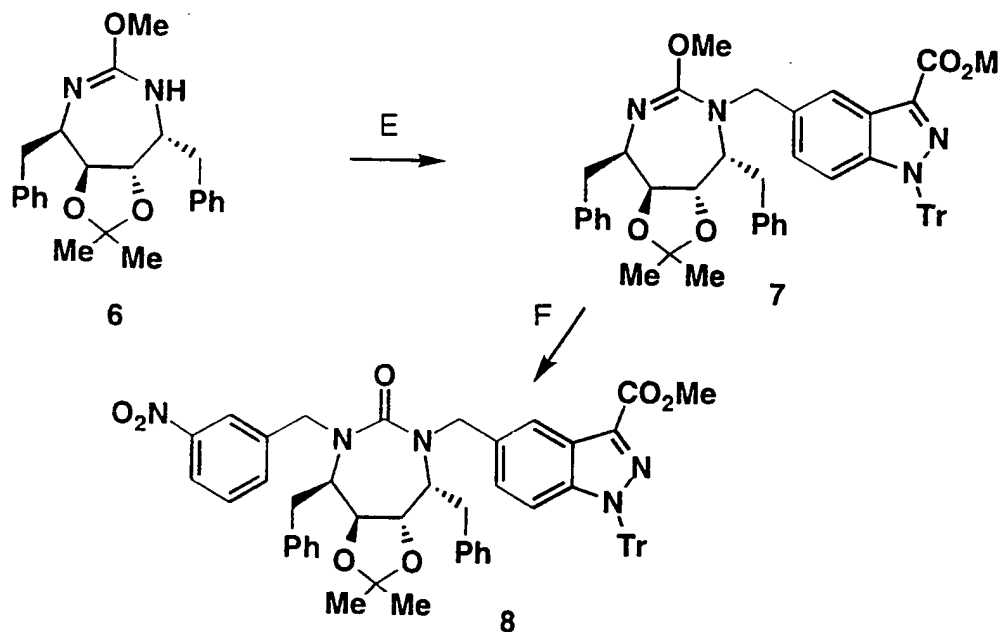
Method B: A solution of 2 (59.0 g, 335 mmol) and concentrated H₂SO₄ (4 mL) in methanol (500 mL) was refluxed over night. The reaction was poured into water (2500 mL) and the precipitate was filtered which gave 53.7 g of 3 as a yellow powder (84%): mp 178-9°C; mass spec. 191 (M+H).

20

Method C: To a chilled (0°C) solution of 3 (32.0 g, 168 mmole) and tritylchloride (56.3 g, 202 mmole) in THF (110 mL) was added NaH (8.76 g, 219 mmole). The reaction was stirred over night while allowed to slowly warm to room temperature. It was diluted with dichloromethane (200 mL) and washed with water (2x100 mL) and saturated NaCl (30 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a brown oil that crystallized on standing. Recrystallization from

methanol/dichloromethane gave 62.9 g of **4** as yellow prisms (87%): mp 192-3°C; mass spec. 433.1 (M+H).

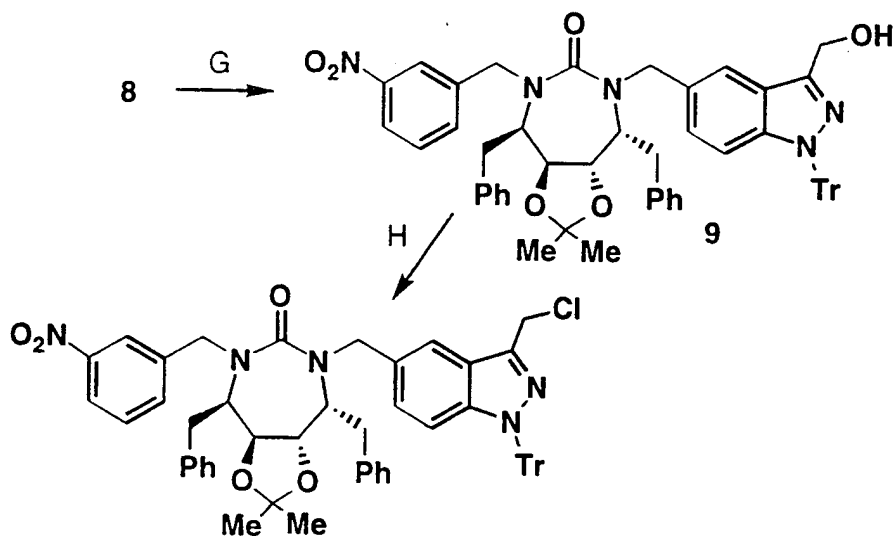
Method D: A mixture of **4** (11.2 g, 25.9 mmole), NBS (4.58 g, 25.9 mmol) and benzoyl peroxide (301 mg, 1.24 mmole) in degassed carbon tetrachloride (100 mL) was refluxed for one hour. Refluxing was stopped when a TLC (dichloromethane) of the reaction indicated the starting material (R_f 0.37) was almost gone and dibrominated indazole (R_f 0.48) was starting to form. After cooling to room temperature, the reaction mixture was filtered through celite with carbon tetrachloride and the filtrate evaporated at reduced pressure which gave a yellow oil that crystallized on standing. Recrystallization from ethyl acetate gave 8.99 g of **5** as creamy white prisms (76%): mp 214-5°C; mass spec. 511.2 (M+H).



Method E: To a chilled (0°C) solution of **6** (4.22 g, 11.1 mmole) and **5** (10.0 g, 16.6 mmole) in DMF (40 mL) was added NaH (0.489 g, 12.2 mmole). The reaction was stirred over night while allowed to slowly warm to room temperature. It was diluted with dichloromethane (100 mL), washed with saturated NH_4Cl (1x80 mL), water (2x80 mL) and saturated NaCl (30 mL), dried (MgSO_4) and evaporated at reduced pressure

which gave a creamy white foam. Flash chromatography (hexane/ethyl acetate, 20%) gave 8.08 g of 7 as a white foam (90%): mp 113-4°C; mass spec. 811.6 (M+H).

- 5 **Method F:** A mixture of 7 (4.95 g, 4.95 mmole), *m*-nitrobenzyl chloride (2.55 g, 14.9 mmole) and potassium iodide (0.852 g, 5.16 mmol) in acetonitrile (70 mL) was refluxed over night. The reaction was diluted with ether (60 mL), washed with water (3x40 mL) and saturated NaCl (20 mL),
 10 dried (MgSO₄) and evaporated at reduced pressure which gave a yellow foam. Flash chromatography (dichloromethane/methanol, 0%-5%) gave 4.60 g of 8 as a white foam (99%): mp 126-8°C; mass spec. 932.3 (M+H).



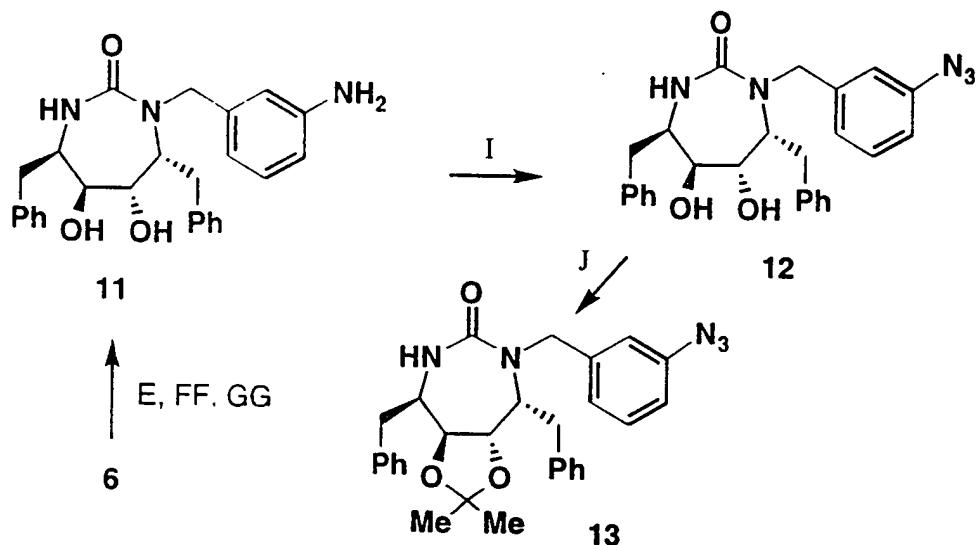
15

10

- Method G:** To a chilled (-78°C) solution of 8 (4.60 g, 4.93 mmole) in dichloromethane (45 mL) was added DIBAL-H (1N in dichloromethane, 11.8 mL, 11.8 mmole) and the reaction was
 20 stirred for 2 hours. After diluting with ether (60 mL), the reaction was washed with 1N HCl (3x40 mL) and saturated NaCl (20 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a light yellow foam. Flash chromatography (hexane/ethyl acetate, 10%) gave 4.18 of 9 as a white foam
 25 (94%): mp 123-5°C; mass spec. 904.7 (M+H).

Method H: To a chilled (0°C) solution of **9** (9.84 g, 10.9 mmole) and diisopropylethylamine (3.01 mL, 17.4 mmol) in DMF (50 mL) was added methanesulfonyl chloride (1.26 mL, 16.3 mmol). After stirring over night, the reaction diluted with ether (100 mL), washed with water (3x50 mL) and saturated NaCl (20 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a light yellow foam. Flash chromatography (dichloromethane) gave 9.88 g of **10** as a creamy white powder (98%): mp 167-8°C; mass spec. 923 (M+H).

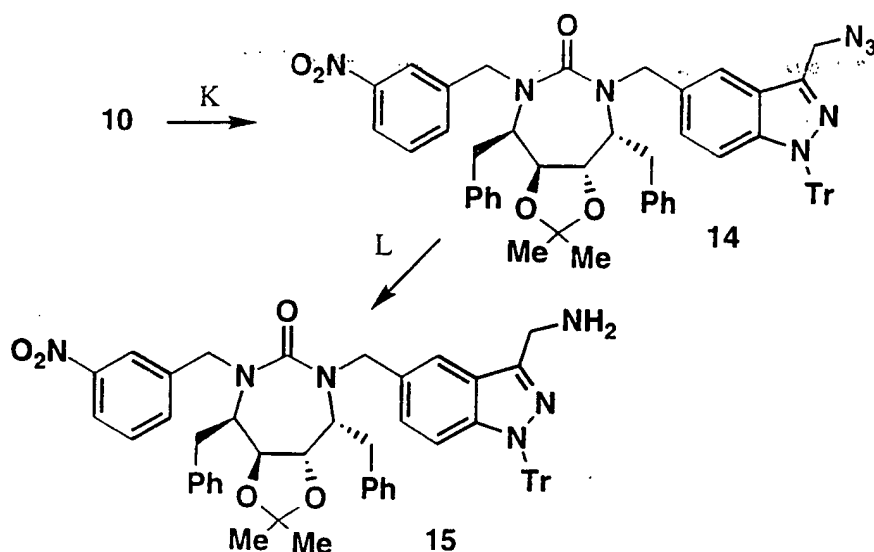
10



Method I: To a chilled (5°C) solution of **11** (2.41 g, 5.59 mmole) in acetic acid (25 mL), was added NaNO₂ (405 mg, 5.87 mmole). After stirring 15 min., NaN₃ was added (400 mg, 6.15 mmol) and the reaction was stirred 30 min. After pouring into water (200 mL), the precipitate was filtered and washed with water (3x30 mL) which gave 2.50 g of **12** as a creamy white powder (98%): mp 173-4°C; mass spec. 458.3 (M+H).

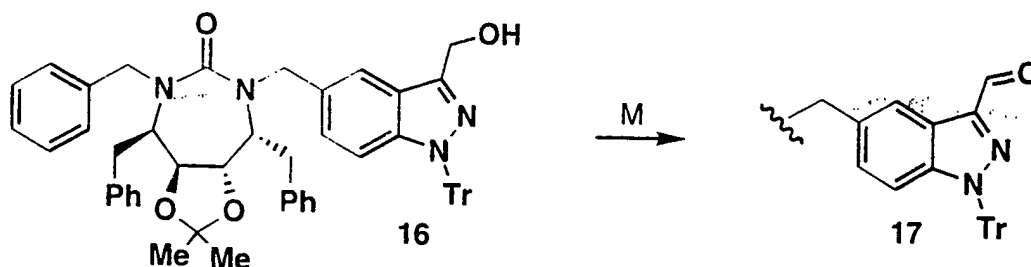
20

Method J: A solution of **12** (2.50 g, 5.477 mmole) was stirred in 2,2-dimethoxypropane (25 mL) with *p*-toluenesulfonic acid monohydrate (31 mg) for 6 hours. The reaction was diluted with ether (60 mL), washed with water (3x30 mL) and saturated NaCl (20 mL), dried (MgSO₄) and evaporated at reduced pressure which gave 2.53 g of **13** as a light yellow foam (99%): mp 52-4°C; mass spec. 498.4 (M+H).



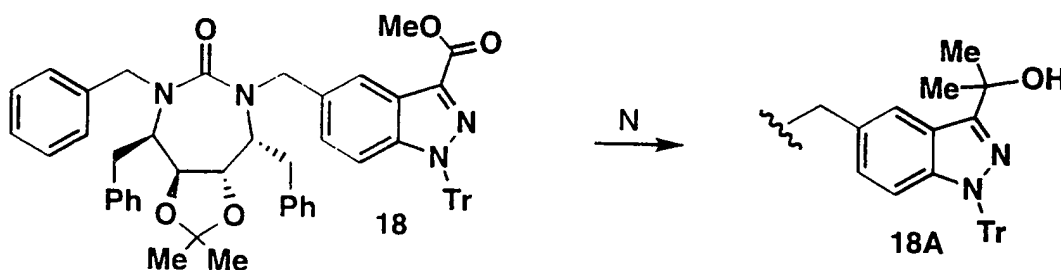
Method K: A solution of **10** (2.10 g, 2.28 mmole) and sodium
 5 azide (178 mg, 2.74 mmol) in DMF (20 mL) was stirred for 2
 hours. The reaction was diluted with ether (50 mL), washed
 with water (3x20 mL) then saturated NaCl (10 mL), dried
 (MgSO₄) and evaporated at reduced pressure which gave 2.08 g
 of **14** as a white powder (98%): mp 110-1°C; mass spec. 930.5
 10 (M+H).

Method L: A solution of **14** (1.60 g, 1.72 mmole),
 triphenylphosphine (540 mg, 2.06 mmole) and 30% NH₄OH (5 mL) in
 THF (20 mL) was stirred over night. The reaction was diluted
 15 with ether (75 mL), washed with water (3x30 mL) and saturated
 NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure
 giving a yellow foam. The foam was dissolved in
 dichloromethane (6 mL), petroleum ether (100 mL) was added
 with stirring and the turbid ether was decanted. The
 20 remaining pasty thick oil was evaporated at reduced pressure
 which gave 1.38 g of **15** as a light creamy white powder (89%):
 mp 98-100°C; mass spec. 903.5 (M+H).

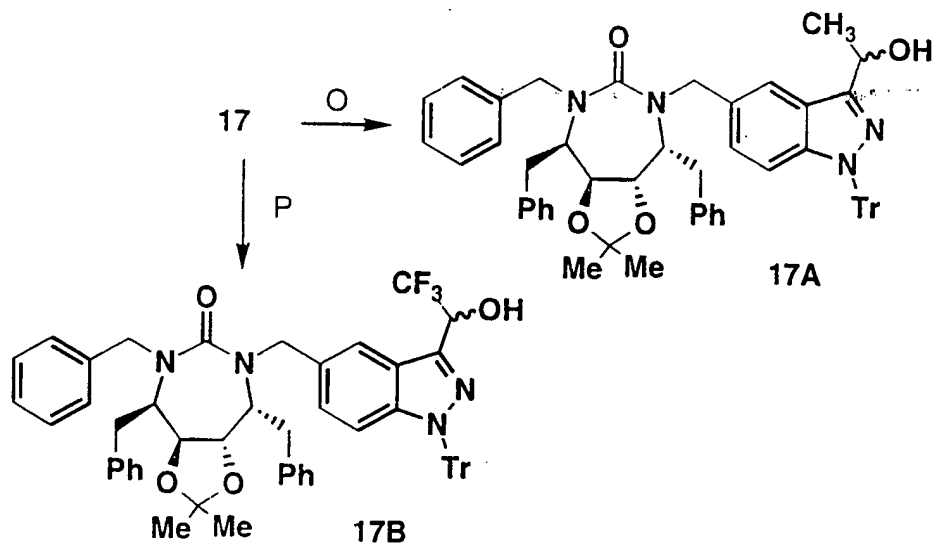


Method M: A mixture of **16** (1.03 g, 1.21 mmol) and MnO₂ (1.12 g, 12.9 mmol) in dichloromethane was stirred over
 5 night. The reaction was filtered through celite with dichloromethane and evaporated at reduced pressure which gave an orange foam. Flash chromatographed (hexane/ethyl acetate 30 %) gave 847 mg of **17** as a white foam (83%): mass spec. 920.8 (M+H).

10

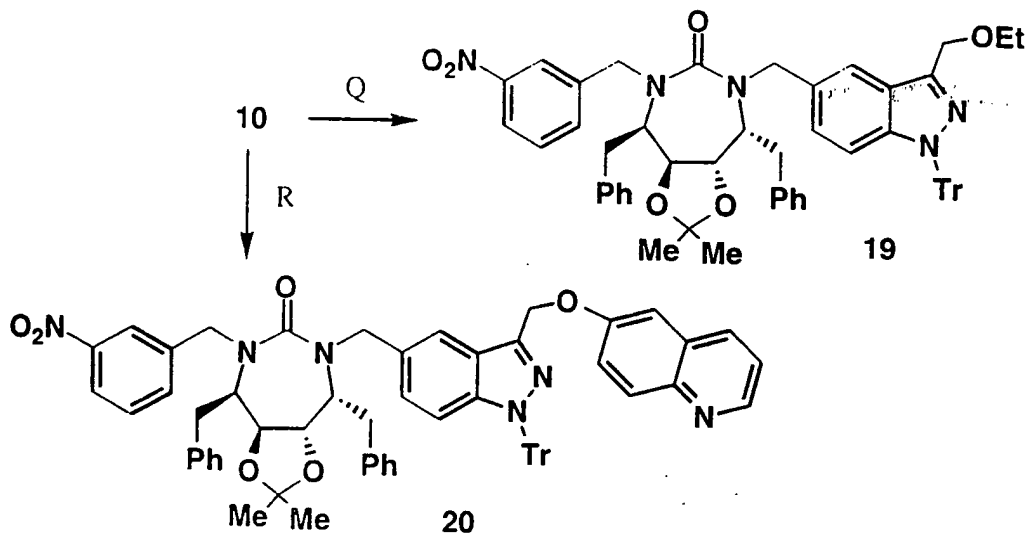


Method N: To a chilled (-78°C) solution of **18** (90 mg, 0.098 mmol) in THF (3 mL) was added MeMgBr (150 mL of 1.4 N in THF, 0.22 mmol). After stirring for 30 min., the reaction was
 15 poured into 1N HCl/ethyl acetate (20 mL/30 mL), washed with water (2x20 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a white film (**18A**) that was carried on to the next reaction without
 20 purification.



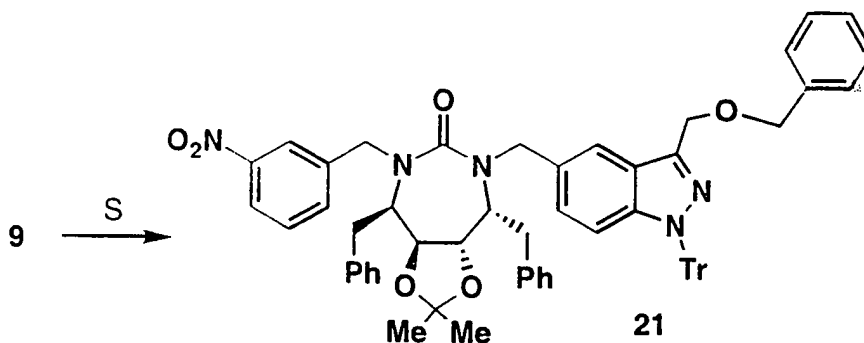
Method O: To a chilled (-78°C) solution of **17** (106 mg, 0.125 mmol) in THF (3 mL) was added MeMgBr (108 mL of 1.4 N in THF, 0.151 mmol). After stirring for 60 min., the reaction was poured into 1N HCl/ethyl acetate (20 mL/30 mL), washed with water (2x20 mL) and saturated NaCl (10 mL), dried (MgSO_4) and evaporated at reduced pressure which gave a white powder (**17A**) that was carried on to the next reaction without purification.

Method P: To a chilled (0°C) solution of **17** (221 mg, 0.250 mmol) and TMS-trifluoromethane (32 mL, 0.300 mmol) in THF (3 mL) was added TBAF (15 mL of 1 N in THF, 0.015 mmol). After stirring for 30 min., 1 N HCl was added (5 mL). After stirring for an additional 15 min., the reaction was diluted with ethyl acetate (30 mL), washed with water (3x20 mL) and saturated NaCl (10 mL), dried (MgSO_4) and evaporated at reduced pressure which gave a yellow oil (**17B**) that was carried on to the next reaction without purification.

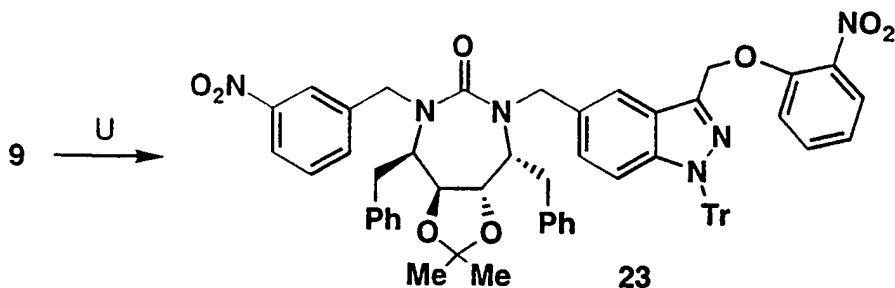
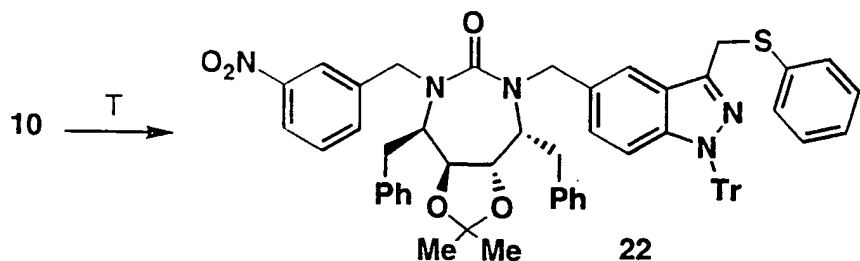


Method Q: To a solution of **10** (2.95 g, 3.20 mmole) and ethanol (0.220 mL, 4.80 mmole) in DMF (15 mL) was added sodium hydride (192 mg, 4.80 mmole). After stirring for two h, the reaction was diluted with ether (80 mL), washed with water (3x50 mL) and saturated NaCl (20 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a light brown foam (**19**) that was carried on to the next reaction without purification.

Method R: To a solution of **10** (2.61 g, 2.86 mmole) and 6-hydroxyquinoline (1.25 g, 8.59 mmole) in DMF (25 mL) was added sodium hydride (172 mg, 4.29 mmole). After stirring over night, the reaction was diluted with ether (100 mL), washed with water (3x50 mL) and saturated NaCl (20 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a creamy white foam (**20**) that was carried on to the next reaction without purification.



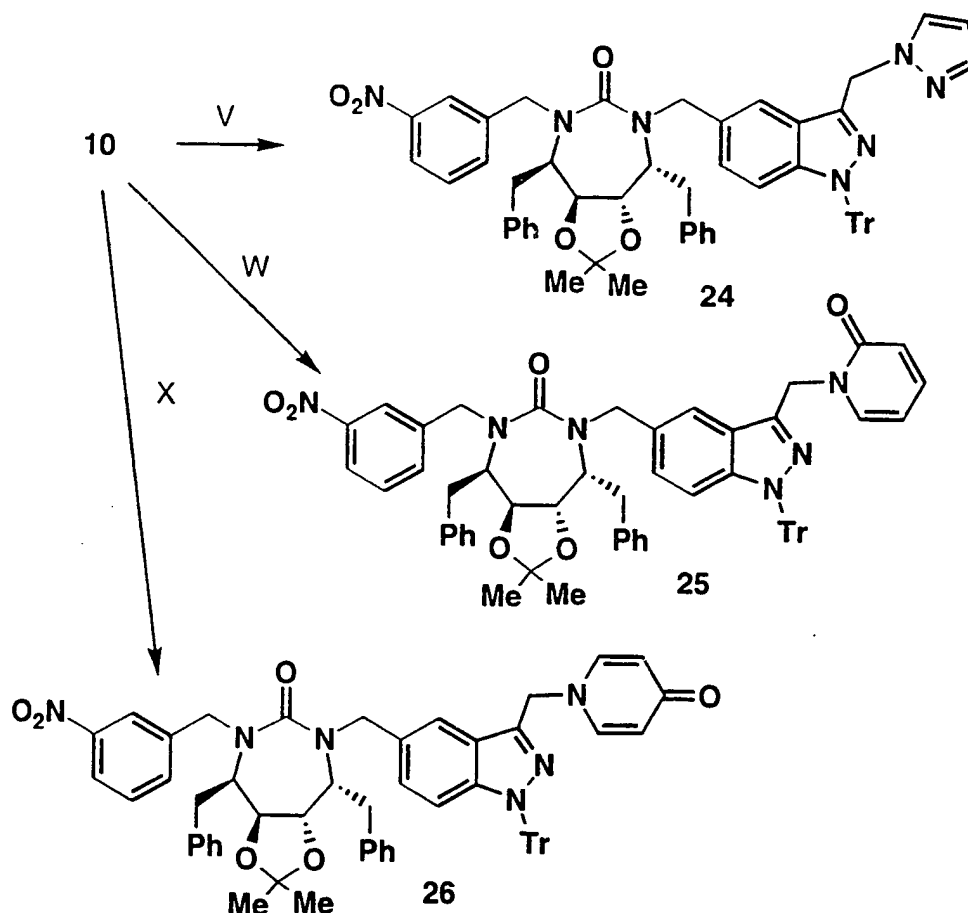
Method S: To a solution of 9 (163 mg, 0.183 mmole) and benzyl bromide (43 mL, 0.365 mmole) in DMF (3 mL) was added sodium hydride (11 mg, 0.275 mmole). After stirring 3 h, the reaction was diluted with ether (30 mL), washed with water (3x20 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a white foam (21) that was carried on to the next reaction without purification.



Method T: To a solution of 10 (181 mg, 0.199 mmole) and thiophenol (41 mL, 0.397 mmole) in DMF (3 mL) was added sodium hydride (12 mg, 0.299 mmole). After stirring 2 h, the reaction was diluted with ether (30 mL), washed with water (3x20 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a tan foam (22)

that was carried on to the next reaction without purification.

Method U: To a solution of **9** (195 mg, 0.218 mmole) and o-fluoronitrobenzene (69 mL, 0.655 mmole) in DMF (3 mL) was added sodium hydride (13 mg, 0.328 mmole). After stirring 1.5 h, the reaction was diluted with ether (30 mL), washed with water (3x20 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a yellow film (**23**) that was carried on to the next reaction without purification.



15 **Method V:** To a solution of **10** (2.99 g, 3.24 mmole) and pyrazole (265 mg, 3.89 mmole) in DMF (30 mL) was added sodium hydride (143 mg, 3.57 mmole). After stirring 1 h, the reaction was diluted with ether (100 mL), washed with water

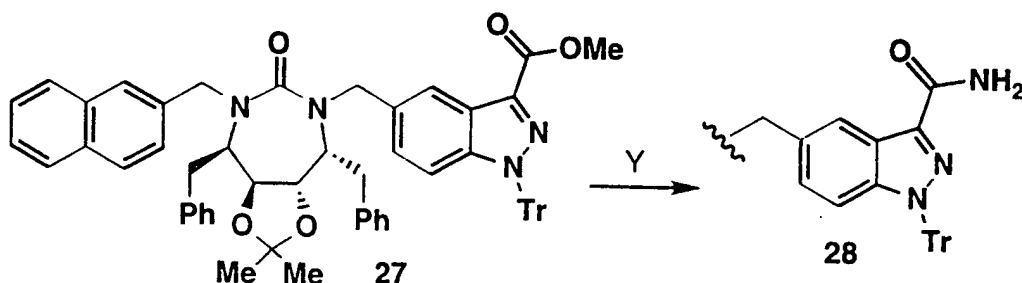
(3x50 mL) and saturated NaCl (20 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a white foam (24) that was carried on to the next reaction without purification.

5

Method W: A solution of 10 (152 mg, 165 mmol) and 2-methoxypyridine (35 mL, 330 mmol) in DMF (3 mL) was stirred over night at 100°C). The reaction was diluted with ether (25 mL), washed with 0.5 N HCl (3x10 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave an orange foam (25) that was carried on to the next reaction without purification.

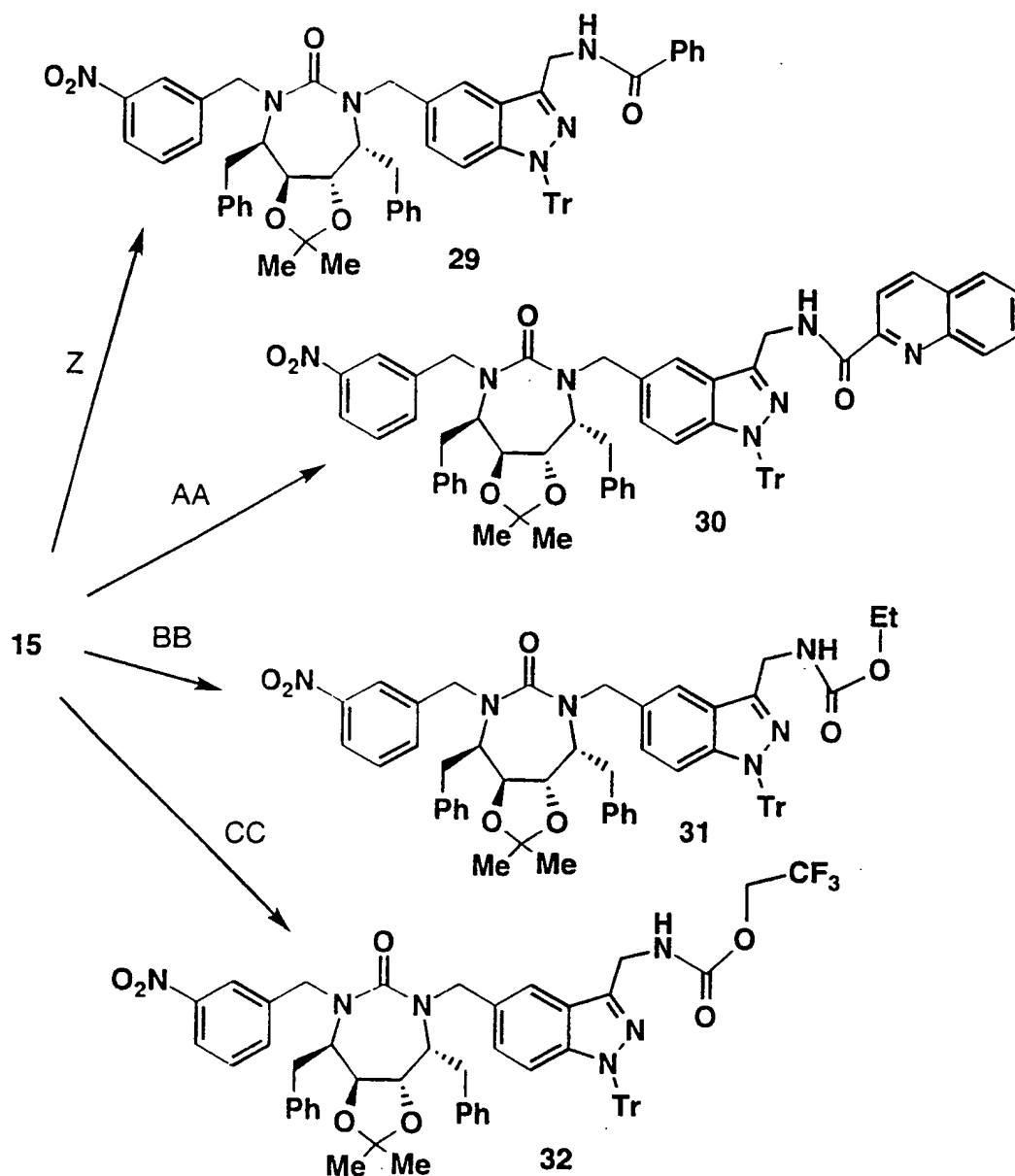
Method X: A solution of the urea 10 (182 mg, 197 mmol), excess K₂CO₃ and 4-hydroxypyridine (38 mL, 395 mmol) in DMF (3 mL) was stirred over night. The reaction was diluted with ether (25 mL), washed with water (3x10 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a yellow oil (26) that was carried on to the next reaction without purification.

20



Method Y: Ammonia (~5 mL condensed) was bubbled with stirring into a chilled solution (-78°C) of trimethyl aluminum (5.21 mmol) in dichloromethane (15 mL). After warming to room temperature and stirring for one hour, 27 was added. After stirring at 35°C over night, the reaction was diluted with ether (70 mL), washed with 1 N HCl (3x30 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a white foam (28) that was carried on to the next reaction without purification.

30



- 5 **Method Z:** To a solution of 15 (3.00 g, 2.66 mmole) and diisopropylethylamine (555 mL, 3.19 mmol) in dichloromethane (30 mL) was added benzoyl chloride (338 mL, 2.93 mmole). After stirring 1 h, the reaction was diluted with ether (80 mL), washed with 0.5 N HCl (2x30 mL), saturated NaHCO₃ (2x30 mL) and saturated NaCl (20 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a white foam (29) that was carried on to the next reaction without purification.
- 10

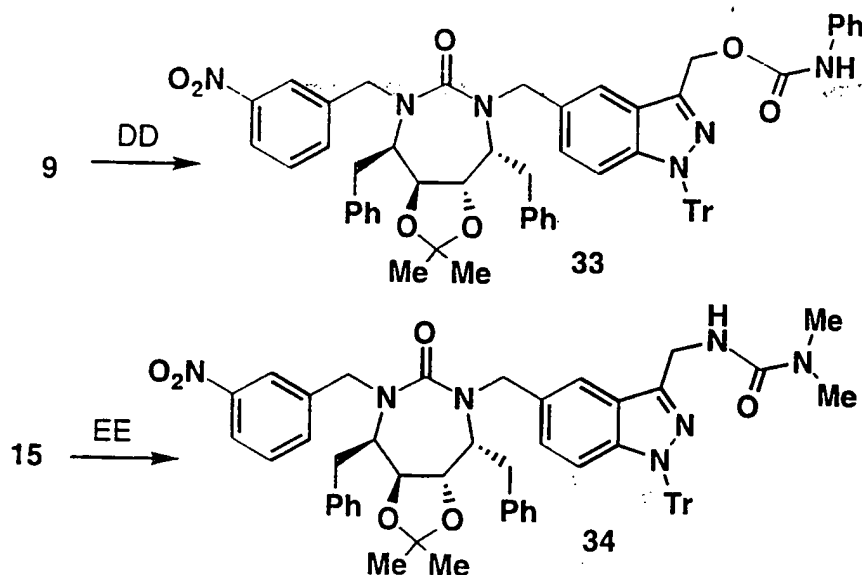
Method AA: A solution of **15** (178 mg, 0.197 mmole), 2-quinoline carboxylic acid (41 mg, 0.237 mmol) and EDC (42 mL, 3.19 mmol) in dichloromethane (3 mL) was stirred over night.
5 The reaction was diluted with ether (30 mL), washed with 0.5 N HCl (2x10 mL), saturated NaHCO₃ (2x10 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a yellow powder (**30**) that was carried on to the next reaction without purification.

10

Method BB: To a solution of **15** (2.01 g, 2.23 mmol) and diisopropylethylamine (504 mL, 2.90 mmol) was added ethyl chloroformate (254 mL, 2.67 mmol). After stirring 30 min., the reaction was diluted with ether (25 mL), washed with 0.5
15 N HCl (2x10 mL), saturated NaHCO₃ (2x10 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a creamy white powder (**31**) that was carried on to the next reaction without purification.

20 **Method CC:** To a solution of 2,2,2-trifluoroethanol (13. mL, 176 mmol) and diisopropylethylamine (31 mL, 176 mmol) in dichloromethane (3 mL) was added *p*-nitrophenyl chloroformate (35.8 mg, 176 mmole). After stirring 15 min., **15** (137 mg, 152 mmol) was added. After stirring over night, the reaction
25 was diluted with ether (25 mL), washed with 0.5 N HCl (2x10 mL), saturated NaHCO₃ (2x10 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave an orange oil (**32**) that was carried on to the next reaction without purification.

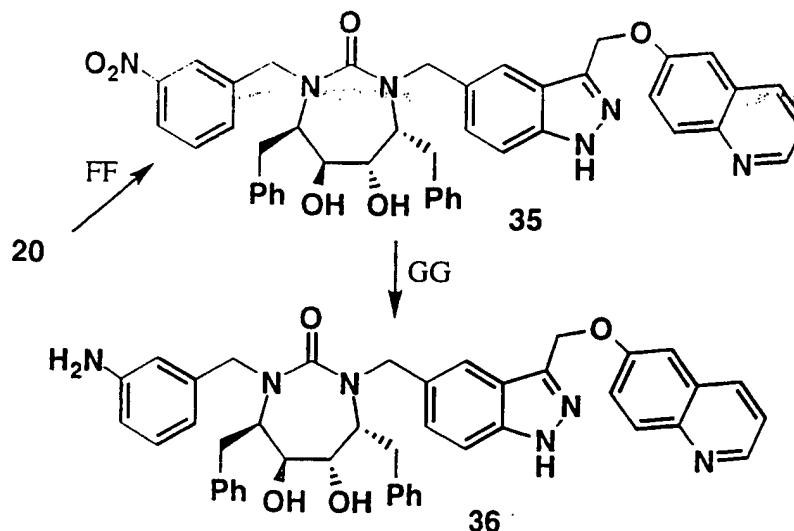
30



Method DD: A solution of **9** (156 mg, 173 mmol), phenylisocyanate (23 mL, 207 mmol) and diisopropylethylamine (30 mL, 173 mmol) in dichloromethane (3 mL) was stirred over night. The reaction was diluted with ether (25 mL), washed with 0.5 N HCl (3x10 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure giving a white powder (**33**) which was carried on to the next reaction without purification.

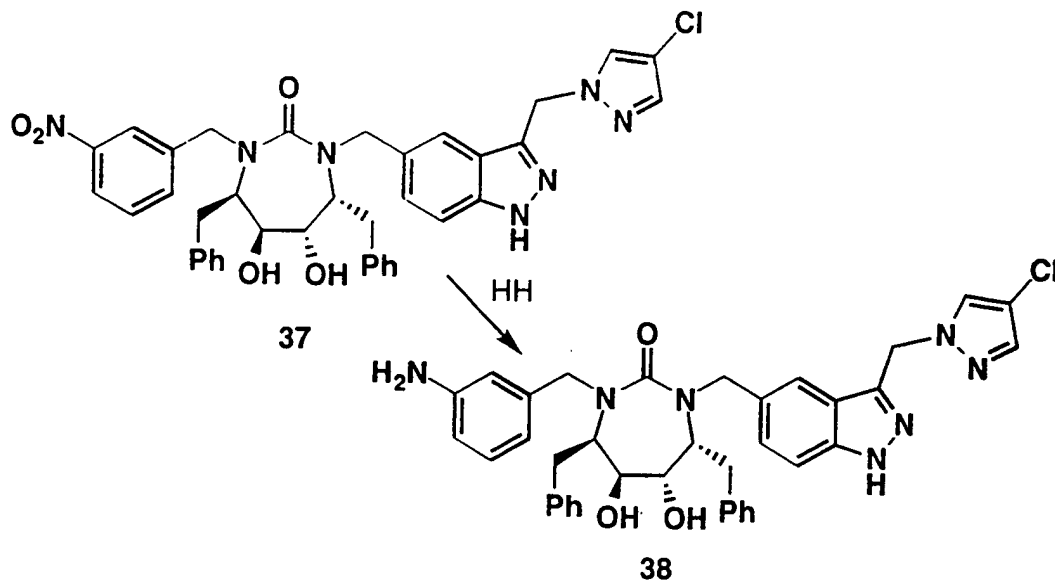
Method EE: To a solution of **15** (154 mg, 171 mmol) and diisopropylethylamine (89 mL, 513 mmol) in dichloromethane (3 mL) was added N,N-dimethylcarbamoyl chloride (31 mL, 341 mmol). After stirring 1.5 h, the reaction was diluted with ether (25 mL), washed with 0.5 N HCl (3x10 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a white powder (**34**) that was carried on to the next reaction without purification.

20



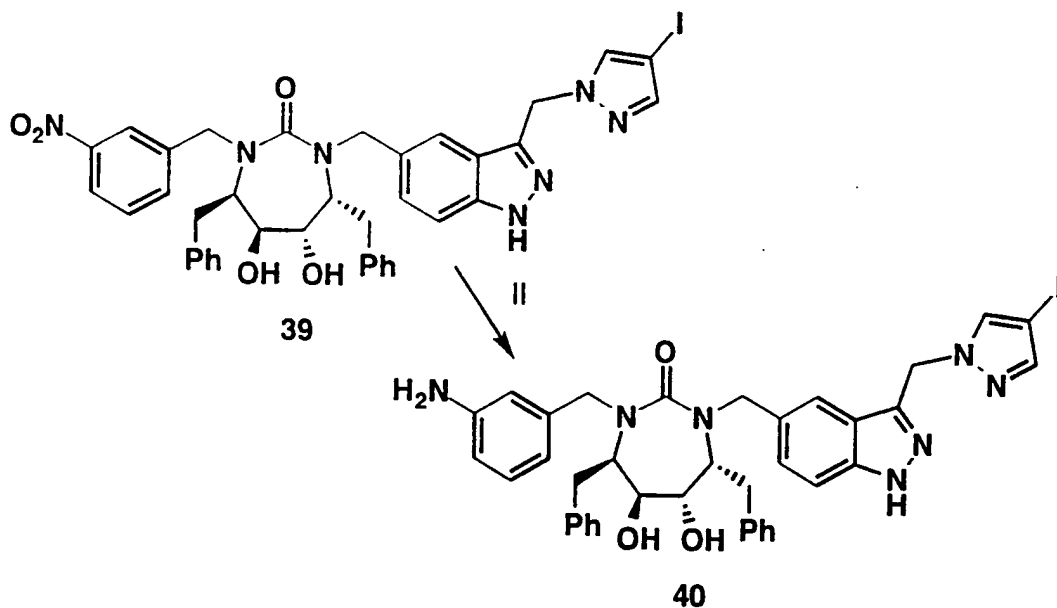
Method FF: A solution of **20** (2.86 mmole) in dichloromethane/TFA (20%, 20 mL) was stirred 2 hours. The reaction was diluted with ether (100 mL), washed with saturated NaHCO_3 (3x40 mL) and saturated NaCl (20 mL), dried (MgSO_4) and evaporated at reduced pressure which gave a creamy white foam (**35**) that was carried on to the next reaction without purification.

Method GG: A mixture of **35** (805 mg, 1.08 mmole), Pd/C (10%, 161 mg) and ammonium formate (81 mg, 1.29 mmol) in methanol (15 mL) was stirred 6 hours. The reaction was filtered through celite with methanol. The filtrate was diluted with ether (100 mL), washed with water (3x50 mL) and saturated NaCl (20 mL), dried (MgSO_4) and evaporated at reduced pressure which gave a creamy white foam. Flash chromatography (dichloromethane chloride/methanol, 6%, with 0.1% NH_4OH) gave 626 mg of **36** as a creamy white powder (81% for two steps).

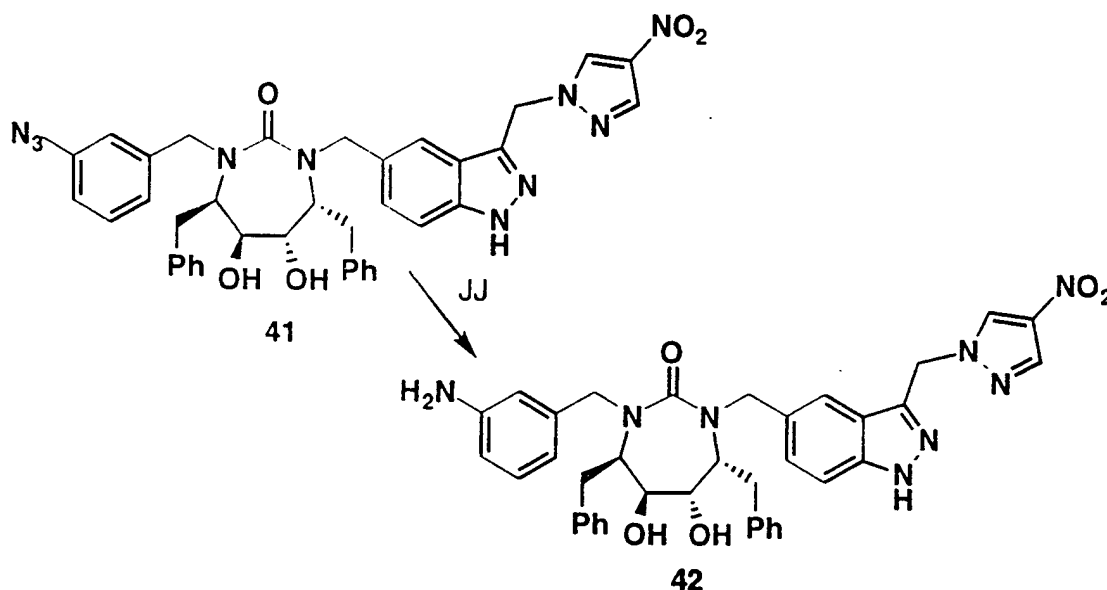


Method HH: A mixture of **37** (3.25 mmole), Zn⁺ (7.90 g, 121 mmol) and calcium chloride (397 mg, 3.58 mmol) in ethanol (30 mL) was refluxed over night. The reaction was filtered
 5 through celite with methanol and the filtrate evaporated at reduced pressure which gave a creamy white powder. Flash chromatography (dichloromethane/methanol, 4%, with 0.1% NH₄OH) gave 1.10 g of **38** as a white powder (50% for three steps).

10

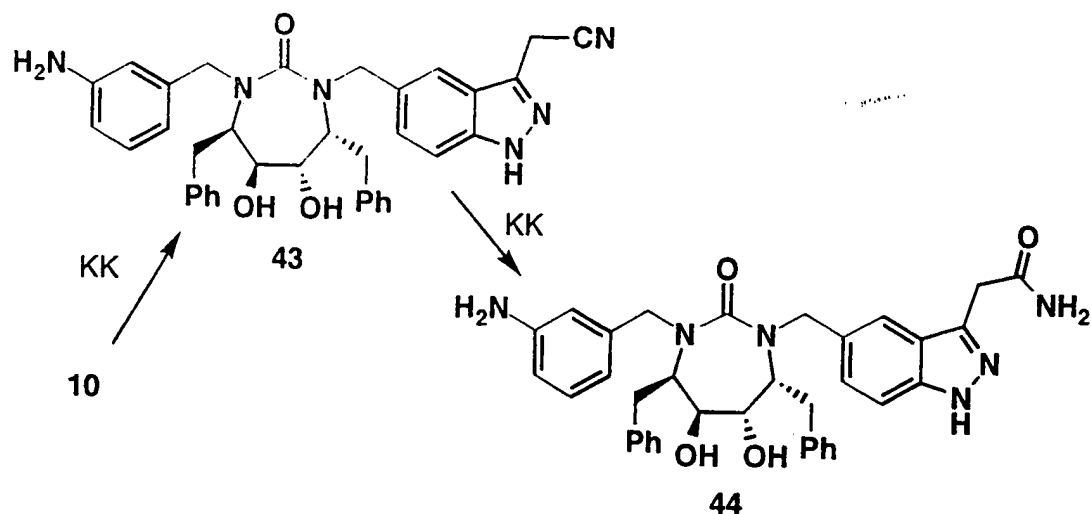


Method II: A mixture of **39** (144 mmole) and tin chloride dihydrate (162 mg, 720 mmol) in ethyl acetate (20 mL) was refluxed for 4 hours. The reaction was diluted with ethyl acetate (20 mL), washed with saturated NaHCO₃ (3x15 mL) and saturated NaCl (20 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a white powder. Flash chromatography (dichloromethane/methanol, 5%, with 0.1% NH₄OH) gave 92 mg of **40** as a white powder (83% for three steps).



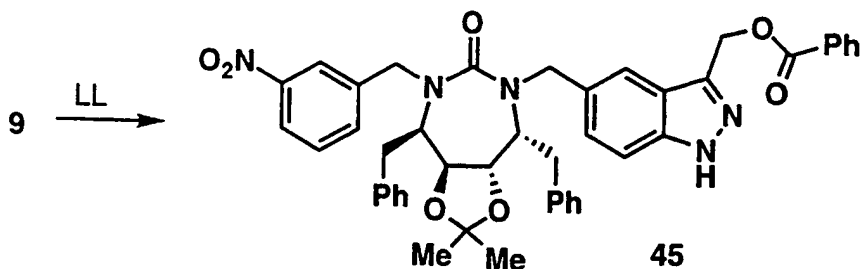
10

Method JJ: A solution of **41** (182 mmole), triphenylphosphine (57 mg, 218 mmole) and 30% NH₄OH (2 mL) in THF (8 mL) was refluxed 4 hours. The reaction was diluted with ether (25 mL), washed with saturated sodium bicarbonate (3x10 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a yellow film. Flash chromatography (dichloromethane/methanol, 5%, with 0.1% NH₄OH) gave 95 mg of **42** as a white powder (64% for three steps).



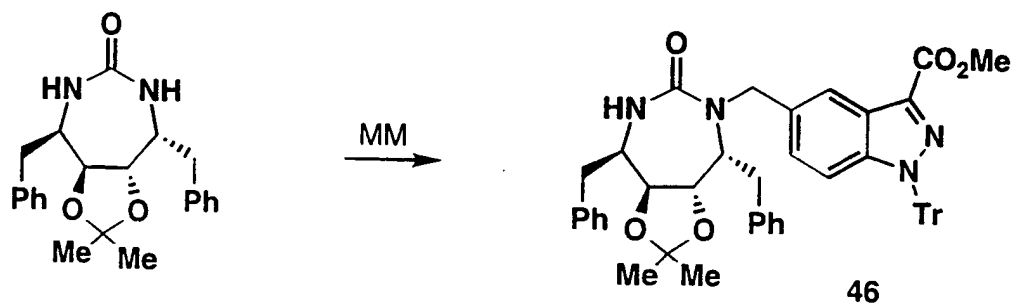
Method KK: A solution of **10** (4.80 g, 5.20 mmol) and KCN (0.407 g, 6.24 mmol) in DMF (50 mL) was stirred overnight. The reaction was added to EtOAc and washed with water (2x), sat. NaCl, dried over Na₂SO₄ and evaporated leaving 4.44 g of a pale yellow foam. This material was deprotected (Method FF) and reduced (Method II) to give **43**.

A mixture of **43** (43 mg, 72 mmol), hydrogen peroxide (30%, 16 mL, 143 mmol) and excess K₂CO₃ in DMSO (5 mL) was stirred 1 hour. The reaction was diluted with ethyl acetate (15 mL), washed with water (3x7 mL) and saturated NaCl (7 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a white powder. Precipitation from dichloromethane/methanol with ether gave 29 mg of **44** as a white powder (65%).

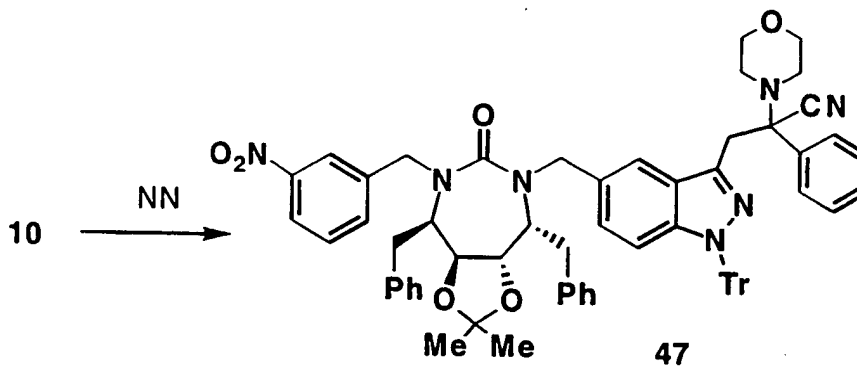


Method LL: To a solution of **9** (161 mg, 0.178 mmole) and diisopropylethylamine (37 mL, 0.214 mmol) in dichloromethane

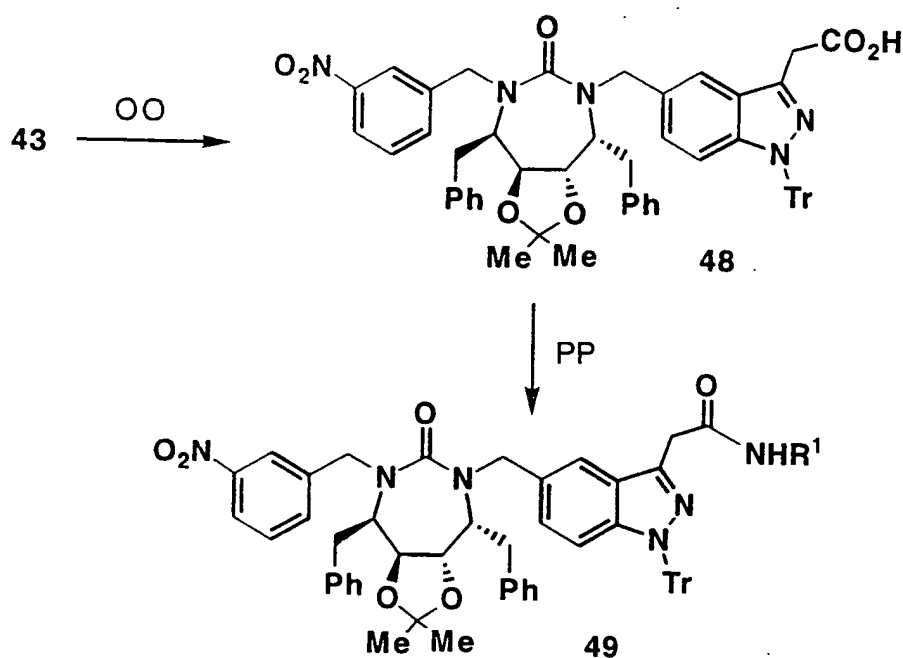
(3 mL) was added benzoyl chloride (23 mL, 0.196 mmole). After stirring 1 h, the reaction was diluted with ether (20 mL), washed with 0.5 N HCl (2x10 mL), saturated NaHCO₃ (2x10 mL) and saturated NaCl (10 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a colorless film (**45**) that was carried on to the next reaction without purification.



Method MM: The starting cyclic urea can be prepared by known methods, e.g., see *Tetr. Lett.* **1995**, 36(28), 4967. To a chilled (0°C) solution of the starting cyclic urea (5.01 g, 14.2 mmole) and **5** (7.27 g, 14.2 mmole) in DMF (40 mL) was added NaH (0.626 g, 15.6 mmole). The reaction was stirred for 1h while allowed to warm to room temperature. After diluting with ether (60 mL), the reaction was washed with saturated NH₄Cl (1x40 mL), water (2x40 mL) and saturated NaCl (20 mL), dried (MgSO₄) and evaporated at reduced pressure which gave a creamy white foam. Flash chromatography (hexane/ethyl acetate, 20-30%) gave 6.95g of **46** as a white foam (63%).



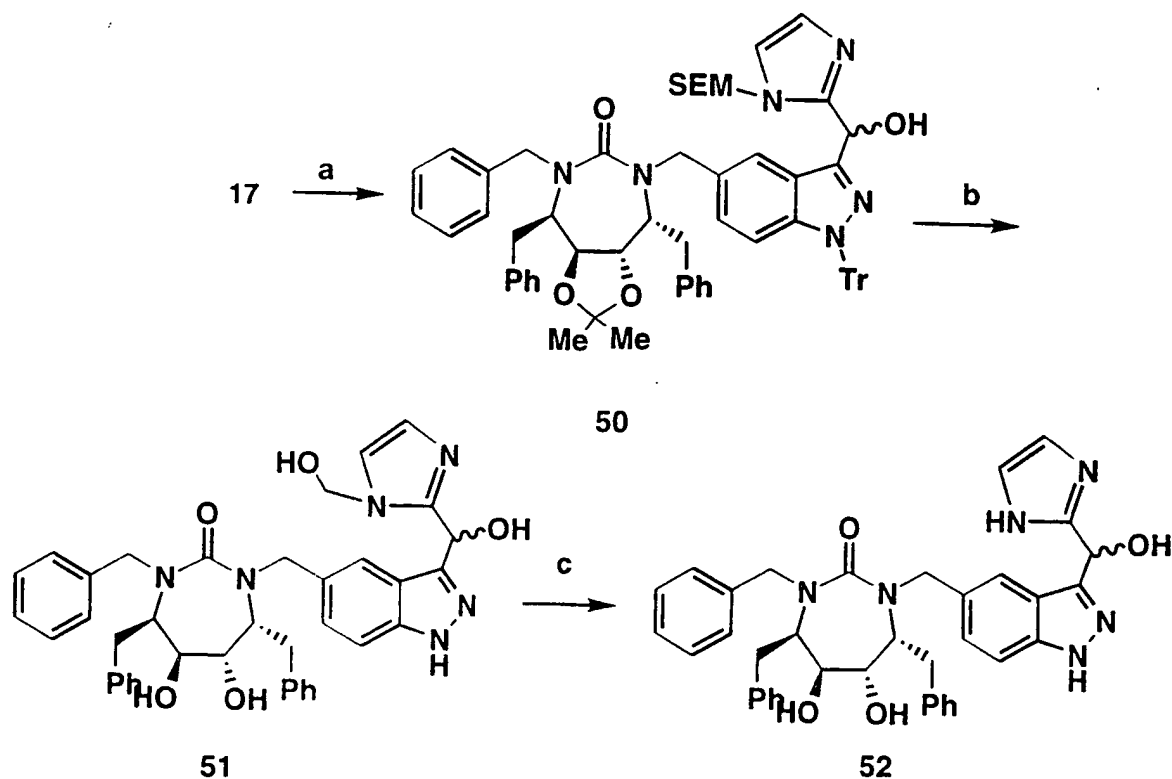
Method NN: To a 0°C solution of the chloride **10** (150 mg, 0.163 mmol) and 2-morpholino-2-phenylacetonitrile (39 mg, 0.195 mmol) in DMF (1 mL), was added NaH (10 mg, 0.244 mmol). After stirring for 2h, the reaction was added to EtOAc and washed with water, sat. NaCl, dried (Na₂SO₄), and evaporated. The resulting white solid was refluxed in EtOH (4 mL) and 3N HCl (1 mL) for 2 h. The reaction was added to EtOAc and washed with sat. NaHCO₃, sat. NaCl, dried (Na₂SO₄) and evaporated leaving 125 mg of a pale yellow glass (**47**) which was used in the next step without further purification.



Method OO: A suspension of the nitrile **43** (2.00g, 2.19 mmol) in EtOH (40 mL) and 25% NaOH (10 mL) was refluxed for 1.5 h. The reaction was added to EtOAc and added washed with sat. NaCl (3X), dried (Na₂SO₄), and evaporated leaving 2.24 g of an orange foam (**48**) which was used without further purification.

Method PP: A solution of **48** (0.161 mmol), amine (1.2 mmol), BOP-Cl (1.2 mmol), and Et₃N (0.322 mmol) in CH₂Cl₂ (2mL) was stirred overnight. The reaction was washed with

sat. NaHCO_3 , sat. NaCl , dried (Na_2SO_4) and evaporated leaving the amide (**49**) which was used without further purification.

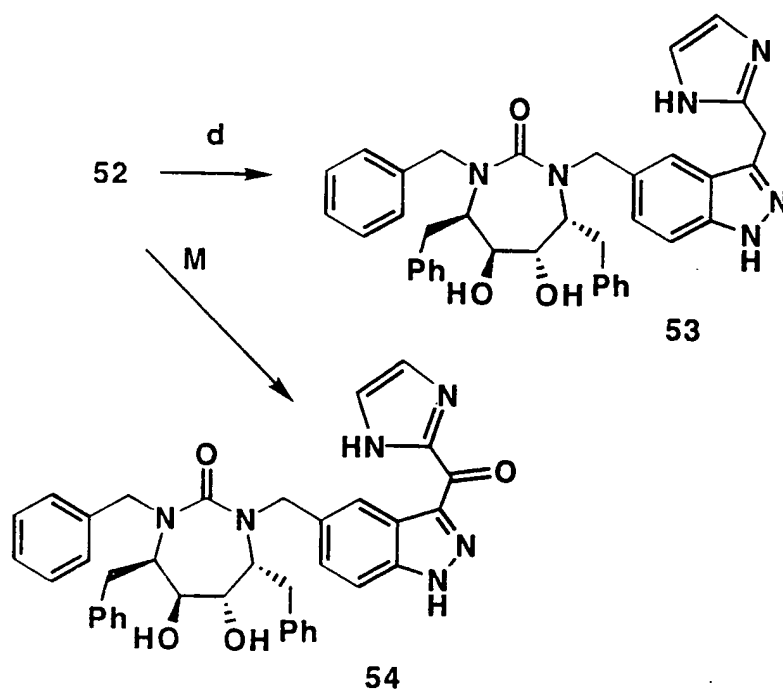


5

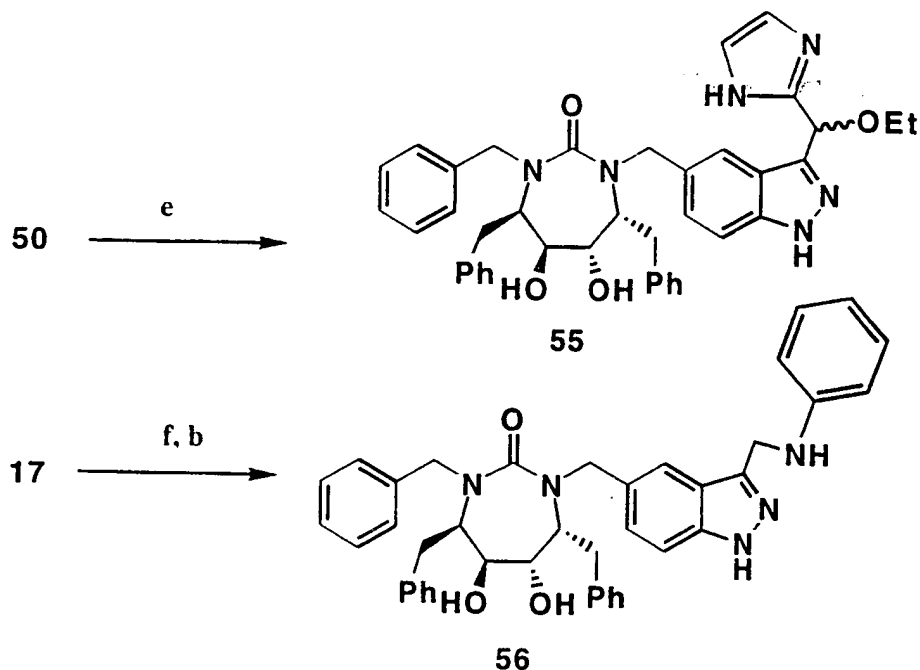
Method a: To a -78°C solution of BuLi (190 μL , 0.467 mmol) in dry ether (2 mL) under argon, was added a solution of SEM-protected imidazole (92 mg, 0.467 mmol) in dry ether (1 mL). After 10 min., a solution of the aldehyde **17** (200 mg, 0.234 mmol) in dry THF (2 mL) was added dropwise (5-15 min.). The reaction was stirred at -78°C for another 10 to 60 minutes and then quenched with saturated NH_4Cl . The reaction was partitioned between EtOAc and saturated NH_4Cl , washed with brine, dried (Na_2SO_4) and evaporated to give an orange oil (**50**) (320 mg, 100% yield).

Method b: A solution of **50** (100 mg) in TFA (1 mL) was stirred for 0.5-12 h at room temperature. The reaction was diluted with EtOAc and neutralized with 10% NaOH , washed with water and brine, dried (Na_2SO_4) and evaporated to give a pale yellow solid (**51**) (85 mg).

Method c: A solution of **51** (1.0 g) in MeOH (10 mL) and 10% NaOH (1 mL) was stirred for 20 min. Ethylene diamine (1 mL) was added, and the reaction was stirred for 5-60 min. The reaction was diluted with EtOAc, neutralized with aqueous HCl, washed with water and brine, dried (Na₂SO₄) and evaporated to give a pale yellow solid. Flash chromatography on silica gel (9% MeOH/CH₂Cl₂) gave a white solid (350 mg) which was triturated with ether to give a white solid (**52**) (330mg).



Method d: A solution of **52** (20 mg) in TFA (1 mL) and Et₃SiH (0.1-0.2 mL) was heated at 60-80 °C overnight. The reaction was diluted with EtOAc, neutralized with 10% NaOH, washed with water and brine, dried (Na₂SO₄) and evaporated to give an orange oil. Flash chromatography on silica gel (8% MeOH/CH₂Cl₂) gave a white semi-solid (17 mg) which was triturated with ether to give a white solid (**53**) (13.5 mg).

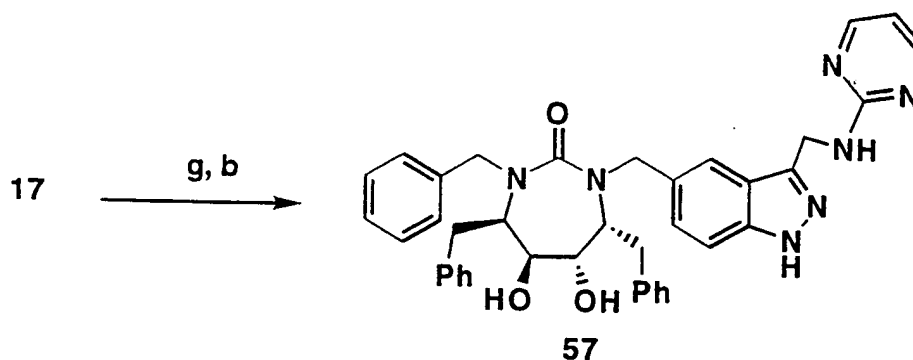


Method e: A solution of **50** (140 mg) in EtOH (2 mL) and 3N HCl (1 mL) was refluxed overnight. The reaction was diluted with EtOAc, neutralized with 10% NaOH, washed with water and brine, dried (Na₂SO₄) and evaporated to give an orange oil. Flash chromatography (8% MeOH/CH₂Cl₂) gave a white glass (20 mg) which was triturated with ether to give a pale orange solid (**55**) (15.8 mg).

10

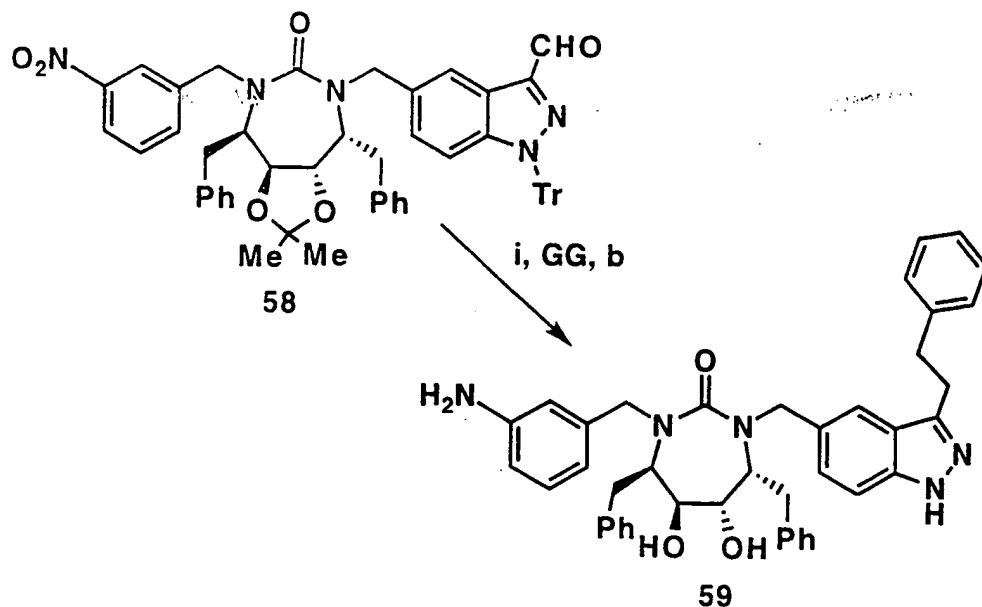
Method f: A mixture of **17** (80 mg, 0.09 mmol), aniline (8.5 μ L, 0.09 mmol), AcOH (5.3 μ L, 0.09 mmol) and NaBH₃CN (15 mg) in MeOH (2 mL) was stirred for 2 h. The reaction was diluted with EtOAc, washed with saturated sodium bicarbonate (2x) and brine, dried (Na₂SO₄) and evaporated to give a pale yellow glass (**56**).

15



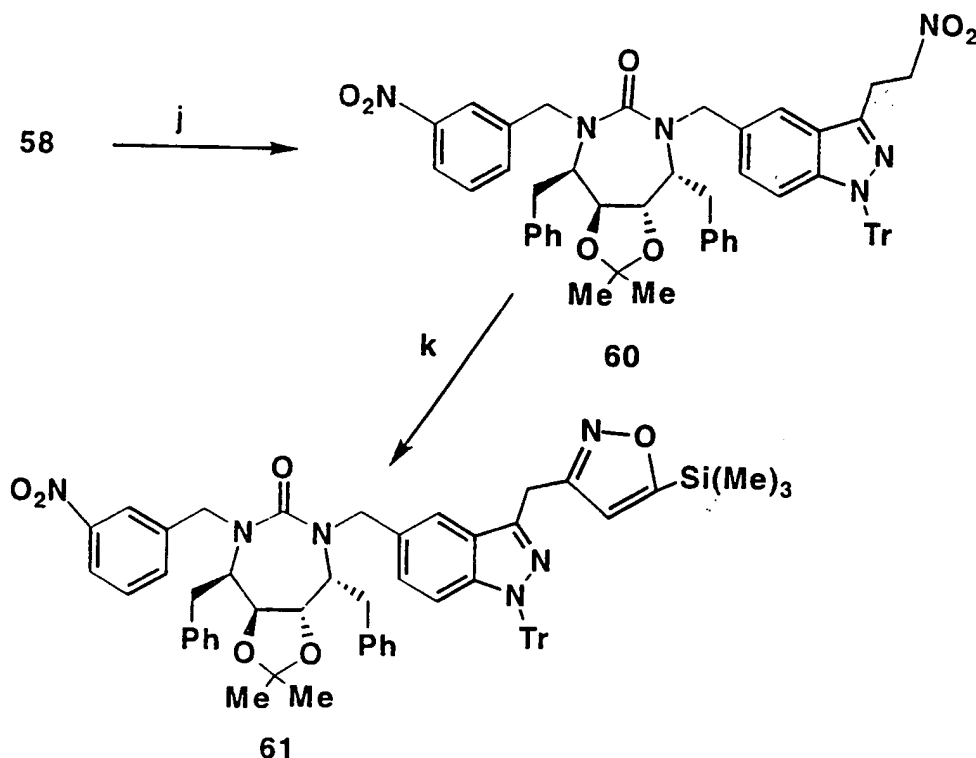
Method g: A solution of **17** (79 mg, 0.09 mmol), 2-aminopyrimidine (7 mg, 0.09 mmol) and benzotriazole (11 mg, 0.09 mmol) in toluene (2 mL) was refluxed for 3.5 h. The solvent was evaporated, and the residue was refluxed in THF with excess of NaBH₄ overnight. The reaction was diluted with EtOAc washed with 10% NaOH (2x), water and brine, dried (Na₂SO₄) and evaporated to give pale yellow glass. Flash chromatography (25-35% EtOAc/hexane) gave a glass (**57**) (22 mg).

Method h: A modified Method R. A suspension of the chloride (**10**) (200 mg, 0.164 mmol), 4-hydroxyacetophenone (45 mg, 0.328 mmol) and potassium carbonate (50 mg) was in ACN (2 mL) refluxed for 5.5 h. The reaction was diluted with EtOAc washed with 10% NaOH (2x), water, brine, dried (Na₂SO₄) and evaporated to give a colorless glass (220 mg, 100% yield).



Method i: To a 0°C suspension of benzyl triphenylphosphonium chloride (86 mg, 0.22 mmol) in THF (2 mL) was added a solution of potassium t-butoxide in THF (0.24 mL, 0.24 mmol). An orange colored ylide formed immediately. After 10 min., a solution of the aldehyde (**58**) (200 mg, 0.22 mmol) in THF (2 mL) was added. The orange color turned slightly yellow after 1 h. TLC (30% EtOAc/hexane) indicated no more starting material (the aldehyde). The reaction was diluted with EtOAc, washed with water (2x), brine, dried (Na₂SO₄) and evaporated to give a white solid (266 mg) which was recrystallized from EtOH to give a white solid (**59**) (100 mg).

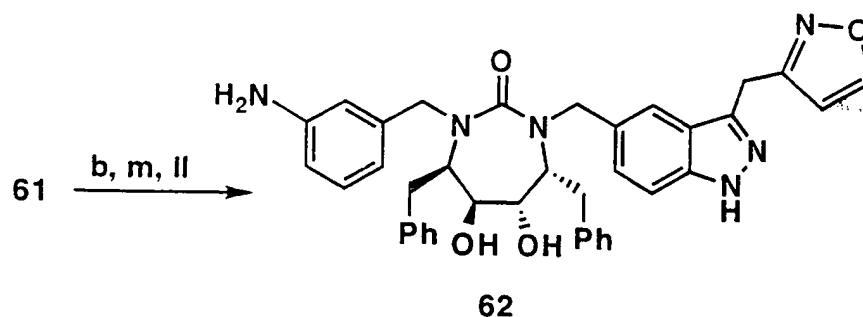
15



Method j: A mixture of (58) (2.5 g), nitromethane (25 mL) and ammonium acetate (0.5 g) was refluxed for 2.5 h. The reaction was diluted with EtOAc washed with water (2x),
 5 brine, dried (Na₂SO₄) and evaporated to give a yellow solid (3.23 g).

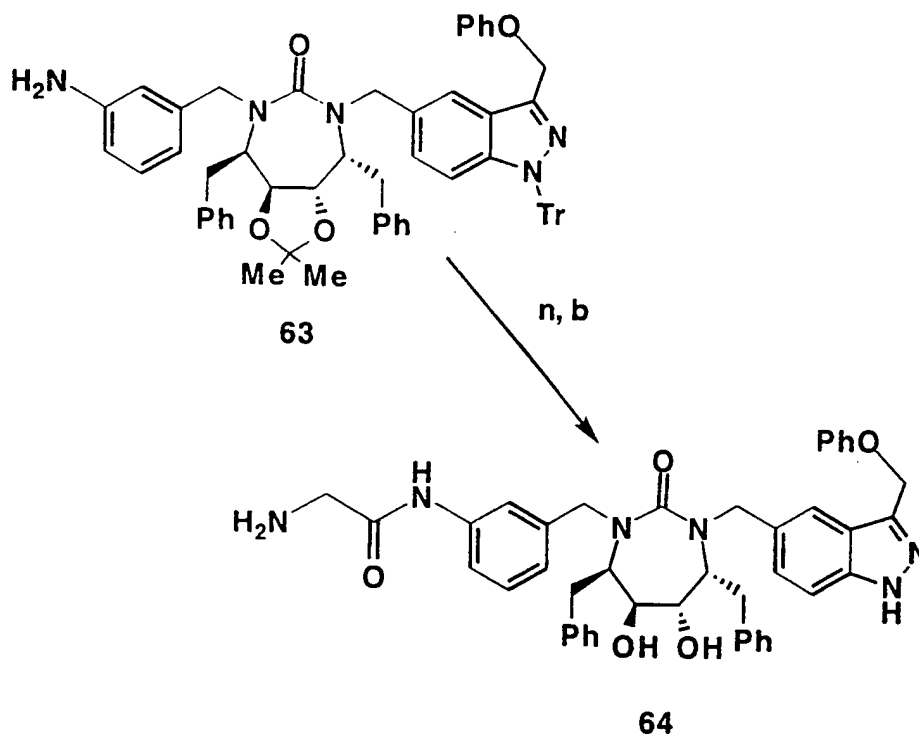
A solution of the nitroethene (3.2 g) and NaBH₄ (0.32 g) in MeOH (75 mL) was stirred for 40 minutes. The reaction was diluted with EtOAc washed with water, brine, dried (Na₂SO₄)
 10 and evaporated to give a yellow solid/glass (3.3 g).
 Chromatography (30% EtOAc/hexane) gave 60 (1.41 g).

Method k: To a solution of the nitroethane (60) (105 mg, 0.11 mmol) in benzene (2 mL) was added PhNCO (72 μ L, 0.66
 15 mmol), TMS-acetylene (63 μ L, 0.44 mmol) and Et₃N (3 drops).
 After stirring at room temperature for 3 h, the reaction was heated to 50°C for 2.5 h, and filtered through celite. The filtrate was diluted with EtOAc, washed with water, saturated NaHCO₃, brine, dried (Na₂SO₄) and evaporated to give a glass.
 20 Flash chromatography (1% MeOH/CH₂Cl₂) gave (61).



Method m: A solution of 5-TMS-isoxazole (100 mg) in EtOH (5 mL) and concentrated ammonia (2 mL) was refluxed for 7.5 h.

- 5 The reaction was diluted with EtOAc, washed with water (2x), brine, dried (Na_2SO_4) and evaporated to give an orange glass (62) (105 mg).



10

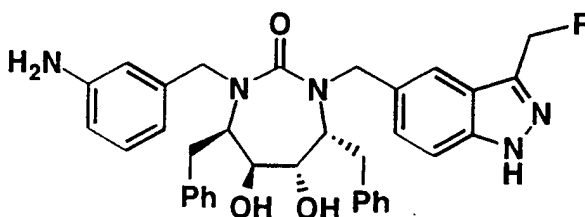
- Method n:** A solution of the aniline (63) (6.3 g, 6.4 mmol), Boc-glycine (2.0 g, 11.6 mmol), BOP-Cl (2.5 g, 10.2 mmol) and Et_3N (1.8 mL, 12.7 mmol) in methylene chloride (60 mL) was stirred overnight. The reaction was diluted with methylene chloride, washed with saturated NaHCO_3 (2x), brine, dried (Na_2SO_4) and evaporated to give a white solid (64) (7.7 g),
- 15

which was carried on to next step reaction without purification.

Table 1 contains representative examples which were made via the methods indicated.

5

Table 1



Ex. #	R	Methods Used	MP (°C)	MS (M+H)
1	phenylmethoxy	S, FF, GG	109-11	682.6
2	phenylthio	T, FF, HH	122-3	684.6
3	hydroxy	G, FF, GG	144-6	592.5
4	2-benzimidazolylthio	T, FF, HH	164-6	724.7
5	2-quinolinylmethoxy	S, FF, GG	126-7	733.6
6	4-trifluoromethylphenoxy	R, FF, GG	124-5	736.7
7	6-quinolinoxy	R, FF, GG	144-5	719.7
8	5-quinolinoxy	R, FF, GG	147-9	719.7
9	4-quinolinoxy	R, FF, GG	177-8	719.7
10	2-methylphenoxy	R, FF, GG	251-2	682.6
11	3-fluorophenylmethoxy	S, FF, GG	188-9	700.6
12	2-fluorophenylmethoxy	S, FF, GG	101-3	700.6
13	ethoxy	Q, FF, GG	129-30	620.6
14	7-quinolinoxy	R, FF, GG	143-4	719.7
15	4-methylphenylmethoxy	S, FF, GG	117-8	696.7
16	4-trifluoromethylphenylmethoxy	S, FF, GG	124-6	750.7
17	3-methylphenoxy	R, FF, GG	128-9	682.6
18	3-aminophenoxy	R, FF, GG	124-6	683.3
19	2,2,2-trifluoroethoxy	Q, FF, GG	236-7	674.3
20	2-aminophenoxy	U, FF, GG	131-3	683.4
21	3-methylphenylmethoxy	S, FF, GG	104-6	696.2
22	3-trifluoromethylphenylmethoxy	S, FF, GG	97-9	750.3
23	5-(2-methyl)benzthiazoloxo	R, FF, GG	135-7	739.4
24	5-benzthiazoloxo	R, FF, GG	142-4	725.2
25	n-butoxy	Q, FF, GG	107-9	648.4
26	4-cinnolinoxy	R, FF, GG	171-3	720.3
27	4-fluoro-2-aminophenoxy	U, FF, GG	127-9	701.3
28	cyclopropylmethoxy	Q, FF, GG	118-20	646.3
29	cyano	K, FF, II	167-9	601.3
30	methyl carbamoyl	BB, FF, GG	142-3	649.3
31	4-cyano-2-methoxyphenoxy	R, FF, GG	131-2	723.4
32	carboxamido	K, KK, GG	148-9	619.3
33	i-butyl carbamoyl	BB, FF, GG	123-4	691.6
34	methoxy	Q, FF, GG	108-9	606.4
35	1-(5-methyl)indazole	V, FF, GG	147-9	706.4
36	N',N'-dimethyl urea	EE, FF, GG	151-3	662.4

37	ethyl carbamoyl	BB, FF, GG	134-6	663.4
38	cyclopropylmethyl carbamoyl	CC, FF, GG	130-2	689.4
39	N-phenyl carbamate	DD, FF, GG	136-7	711.3
40	1-pyrazole	V, FF, GG	138-9	642.3
41	3-oxazolid-2-one	V, FF, GG	143-4	661.3
42	n-propyl carbamoyl	BB, FF, GG	123-4	677.3
43	3,4-dimethoxyphenoxy	AA, FF, GG	119-20	728.3
44	N'-pyrrolidine urea	EE, FF, GG	166-7	688.3
45	n-butyl carbamoyl	AA, FF, GG	121-2	691.3
46	amino	K, L, FF, GG	164-5	591.2
47	i-propyl carbamoyl	AA, FF, GG	127-8	677.2
48	t-butyl carbamoyl	CC, FF, GG	136-8	691.4
49	trifluoroacetamido	Z, FF, GG	157-8	687.4
50	1-pyrid-2-one	W, FF, GG	145-6	669.5
51	2,2,2-trifluoroethyl carbamoyl	CC, FF, GG	127-8	747.4
52	3-tetrahydrofuranyl carbamoyl	CC, FF, GG	138-9	735.5
53	3-allyl carbamoyl	CC, FF, HH	115-6	675.5
54	1-(4-methyl)pyrazole	V, FF, GG	133-4	656.5
55	1-(4-chloro)pyrazole	V, FF, HH	120-1	676.5
56	1-pyrid-4-one	X, FF, GG	171-2	669.6
57	1-(4-bromo)pyrazole	V, FF, HH	136-7	720.4
58	2-pyridinyl carboxamido	Z, FF, GG	139-40	696.5
59	phenyl carboxamido	Z, FF, GG	143-4	695.5
60	1-(4-amino)pyrazole	V, FF, GG	134-5	657.5
61	1-(3-trifluoromethyl)pyrazole	V, FF, GG	207-8	710.5
62	2-oxetanemethoxy	Q, FF, GG	127-8	662.5
63	1-(3,5-dimethoxy)pyrazole	V, FF, GG	141-2	670.6
64	1-(3-amino)pyrazole	V, FF, GG	138-9	657.6
65	2-furanyl carboxamido	Z, FF, GG	148-9	685.5
66	2-thiophenyl carboxamido	Z, FF, GG	145-6	701.5
67	1-(4-iodo)pyrazole	V, FF, II	206-7	768.3
68	1-(4-nitro)pyrazole	I, J, MM, G, H, V, FF, GG, JJ	214-5	687.5
69	1-(3-nitro)pyrazole	I, J, MM, G, H, V, FF, GG, JJ	148-9	687.5
70	t-butyl carboxamido	Z, FF, GG	141-2	675.6
71	3-trifluoromethylphenyl carboxamido	Z, FF, GG	137-8	763.5
72	3-methoxyphenyl carboxamido	Z, FF, GG	133-4	725.4
73	4-methoxyphenyl carboxamido	Z, FF, GG	148-9	725.4
74	2-quinolinyl carboxamido	AA, FF, GG	153-4	746.4
75	2-pyrazinyl carboxamido	AA, FF, GG	155-6	697.4
76	1-i-quinolinyl carboxamido	AA, FF, GG	149-50	746.5
77	2-methoxyphenyl carboxamido	Z, FF, GG	144-5	725.5
78	1-(4-carboethoxy)pyrazole	V, FF, GG	135-6	714.5
79	benzoyloxy	LL, FF, GG	126-7	696.5
80	2-fluorophenyl carboxamido	Z, FF, GG	138-9	713.4
81	3-fluoro-5-trifluoromethylphenoxy	R, FF, GG	228-9	754.4
82	4-fluorophenyl carboxamido	Z, FF, GG	150-1	713.4
83	8-(1,2,3,4-tertrahydro)quinolinyl carboxamido	AA, FF, GG	152-3	750.4
84	2-(6-methyl)pyridinyl carboxamido	AA, FF, GG	141-2	710.4
85	2-aminophenyl carboxamido	AA, FF, GG	146-7	710.5
86	3-aminophenyl carboxamido	AA, FF, GG	159-60	710.6
87	4-aminophenyl carboxamido	AA, FF, GG	168-9	710.5
88	2,6-difluorophenyl carboxamido	Z, FF, GG	148-50	731.3
89	1-(4-acetyl)pyrazole	V, FF, GG	131-2	684.4
90	1-(4-carbomethoxy)pyrazole	V, FF, GG, B	138-40	700.4

91	2-pyridylmethoxy	R, FF, GG	160	683.4
92	2-methyl-4-thiazolemethoxy	S, FF, HH	(dec.)	
93	propoxy	Q, FF, HH	112-6	703.4
94	N,N-dimethylcarbamoyl	S, FF, HH	112-6	634.5
95	6-methyl-2-pyridylmethoxy	S, FF, GG	134-6	663.6
96	phenoxy	R, FF, HH	110-4	697.7
97	2-isopropyl-4-thiazolemethoxy	S, FF, HH	222-4	668.6
98	4-methylphenoxy	R, FF, GG	97-102	731.6
99	4-methoxyphenoxy	R, FF, GG	114-8	682.6
100	4-cyanophenoxy	R, FF, GG	113-7	698.6
101	phenylsulfonyl	R, FF, II	127-32	693.6
102	2-tetrahydrofuranmethoxy	R, FF, GG	142-47	716.7
103	3-pyridoxy	R, FF, GG	109-13	676.4
104	2-methyl-6-benzothiazoloxo	R, FF, GG	119-23	669.3
105	5-trifluoromethyl-2-pyridylmethoxy	R, FF, GG	132-37	739.4
106	N-methylcarbamoyl	S, FF, GG	112-6	751.3
107	N-isopropylcarbamoyl	DD, FF, GG	125-30	649.3
108	2-methyl-5-pyridoxy	DD, FF, GG	134-9	677.5
109	1,2,4-triazole	R, FF, GG	128-31	683.5
110	benzoyl	R, FF, GG	137-41	643.6
111	N-t-butylcarboxamido	NN, II	189-91	680.5
112	N,N-diethylcarboxamido	PP, FF, GG	142-7	675.5
113	N-phenylcarboxamido	PP, FF, GG	130-34	675.6
114	pyrrolidinecarboxamido	PP, FF, GG	140-4	695.6
115	4-fluorophenoxy	PP, FF, GG	141-5	673.6
		R, FF, GG	120-5	703
116	3-fluorophenoxy			(M+18)
117	4-fluorophenylmethoxy	R, FF, GG	245-8	686.6
118	2-naphthylmethoxy	S, FF, GG	108-11	700.6
119	2-naphthoxy	S, FF, GG	110-15	732.7
		R, FF, GG	174-7	735
120	2-fluorophenoxy			(M+18)
121	4-chlorophenoxy	R, FF, GG	227-30	686.6
122	2,4-di-fluorophenoxy	R, FF, II	136-40	702.6
123	phenyl sulfonamido	R, FF, GG	190-3	704.6
		R, FF, GG	185-90	748
124	4-(methylsulfonyl)phenoxy			(M+18)
125	2-fluoro-3-pyridoxy	R, FF, GG	145-50	746.3
126	2-benzothiazolemethoxy	S, FF, GG	110-15	701.4
127	3-cyanophenoxy	R, FF, GG	124-8	739.2
128	3,4-di-fluorophenoxy	R, FF, GG	121-5	693.4
129	2-piperonyloxy	R, FF, GG	217-21	704.3
130	2-fluoro-4-pyridylmethoxy	R, FF, GG	150-5	712.4
131	6-fluoro-2-pyridylmethoxy	R, FF, GG	110-14	701.3
132	5-chloro-3-pyridoxy	S, FF, GG	108-13	701.3
133	3-chloro-6-pyridazoxy	R, FF, II	121-6	703.2
134	8-quinolinoxy	S, FF, II	142-7	704.3
135	6-chloro-2-pyridylmethoxy	R, FF, GG	147-52	719.4
136	2-chloro-3-pyridoxy	S, FF, II	110-14	717.3
137	3-methoxy-phenoxy	R, FF, II	180-3	703.4
138	2-methoxy-phenoxy	R, FF, GG	241-4	698.3
139	3-furanoxy	R, FF, GG	200-4	698.3
140	3-acetylphenoxy	R, GG, FF	115-20	662.5
141	2-thiazole	R, FF, GG	113-7	710.5
142	2-benzimidazole	a, d, GG	128-31	659.4
143	1-(2-benzimidazole)-1-(OH)	a, d, c, GG	170-5	692.5
		a, d, c, GG		708.5

144	N-methyl-2-imidazole	a,d,GG	125-30	656.5
145	phenylamino	f,b,GG	124-8	667.5
146	4-acetyl phenoxy	h,FF,GG	125-30	710.6
147	6-cyano-2-pyridyl	S,FF,II	110-15	708.6
148	3-pyrazole	a,b,d,c,GG	145-50	642.5
149	2-benzothiazole	a,d,GG	127-30	709.4
150	phenymethyl	i,GG,b	110-15	666.5
151	1-(2-benzothiazole)-1-(OH)	a,d,GG	150-5	725.4
152	2-pyridyl	a,d,GG	130-3	653.5
153	2-isoxazole	j,k,b,m,II	115-20	643.5
154	2-tetrahydrofuran	a,d,GG	125-8	646.5
155	2-furan	a,d,GG	124-7	642.3

Utility

The compounds of formulae I and II possess HIV protease inhibitory activity and are therefore useful as antiviral agents for the treatment of HIV infection and associated diseases. The compounds of formulae I and II possess HIV protease inhibitory activity and are effective as inhibitors of HIV growth. The ability of the compounds of the present invention to inhibit viral growth or infectivity is demonstrated in standard assay of viral growth or infectivity, for example, using the assay described below.

The compounds of formulae I and II of the present invention are also useful for the inhibition of HIV in an *ex vivo* sample containing HIV or expected to be exposed to HIV. Thus, the compounds of the present invention may be used to inhibit HIV present in a body fluid sample (for example, a serum or semen sample) which contains or is suspected to contain or be exposed to HIV.

The compounds provided by this invention are also useful as standard or reference compounds for use in tests or assays for determining the ability of an agent to inhibit viral clone replication and/or HIV protease, for example in a pharmaceutical research program. Thus, the compounds of the present invention may be used as a control or reference compound in such assays and as a quality control standard. The compounds of the present invention may be provided in a commercial kit or container for use as such standard or reference compound.

Since the compounds of the present invention exhibit specificity for HIV protease, the compounds of the present invention may also be useful as diagnostic reagents in diagnostic assays for the detection of HIV protease. Thus, inhibition of the protease activity in an assay (such as the assays described herein) by a compound of the present invention would be indicative of the presence of HIV protease and HIV virus.

As used herein "µg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "µL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "µM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma" stands for the Sigma-Aldrich Corp. of St. Louis, MO.

HIV RNA Assay

DNA Plasmids and in vitro RNA transcripts:

Plasmid pDAB 72 containing both gag and pol sequences of BH10 (bp 113-1816) cloned into PTZ 19R was prepared according to Erickson-Viitanen et al. *AIDS Research and Human Retroviruses* 1989, 5, 577. The plasmid was linearized with Bam HI prior to the generation of in vitro RNA transcripts using the Riboprobe Gemini system II kit (Promega) with T7 RNA polymerase. Synthesized RNA was purified by treatment with RNase free DNase (Promega), phenol-chloroform extraction, and ethanol precipitation. RNA transcripts were dissolved in water, and stored at -70°C. The concentration of RNA was determined from the A260.

Probes:

Biotinylated capture probes were purified by HPLC after synthesis on an Applied Biosystems (Foster City, CA) DNA synthesizer by addition of biotin to the 5' terminal end of the oligonucleotide, using the biotin-phosphoramidite reagent of Cocuzza, Tet. Lett. 1989, 30, 6287. The gag biotinylated capture probe (5-biotin-CTAGCTCCCTGCTTGCCCATACTA 3') was complementary to nucleotides 889-912 of HXB2 and the

pol biotinylated capture probe (5'-biotin
-CCCTATCATTTTGGTTTCCAT 3') was complementary to nucleotides
2374-2395 of HXB2. Alkaline phosphatase conjugated
oligonucleotides used as reporter probes were prepared by
5 Syngene (San Diego, CA.). The pol reporter probe (5'
CTGTCTTACTTTGATAAAACCTC 3') was complementary to nucleotides
2403-2425 of HXB2. The gag reporter probe (5'
CCCAGTATTTGTCTACAGCCTTCT 3') was complementary to nucleotides
950-973 of HXB2. All nucleotide positions are those of the
10 GenBank Genetic Sequence Data Bank as accessed through the
Genetics Computer Group Sequence Analysis Software Package
(Devereau *Nucleic Acids Research* 1984, 12, 387). The
reporter probes were prepared as 0.5 μ M stocks in 2 x SSC
(0.3 M NaCl, 0.03 M sodium citrate), 0.05 M Tris pH 8.8, 1
15 mg/mL BSA. The biotinylated capture probes were prepared as
100 μ M stocks in water.

Streptavidin coated plates:

Streptavidin coated plates were obtained from Du Pont
20 Biotechnology Systems (Boston, MA).

Cells and virus stocks:

MT-2 and MT-4 cells were maintained in RPMI 1640
supplemented with 5% fetal calf serum (FCS) for MT-2 cells or
25 10% FCS for MT-4 cells, 2 mM L-glutamine and 50 μ g/mL
gentamycin, all from Gibco. HIV-1 RF was propagated in MT-4
cells in the same medium. Virus stocks were prepared
approximately 10 days after acute infection of MT-4 cells and
stored as aliquots at -70°C. Infectious titers of HIV-1(RF)
30 stocks were $1-3 \times 10^7$ PFU (plaque forming units)/mL as
measured by plaque assay on MT-2 cells (see below). Each
aliquot of virus stock used for infection was thawed only
once.

For evaluation of antiviral efficacy, cells to be
35 infected were subcultured one day prior to infection. On the
day of infection, cells were resuspended at 5×10^5 cells/mL
in RPMI 1640, 5% FCS for bulk infections or at 2×10^6 /mL in
Dulbecco's modified Eagles medium with 5% FCS for infection

in microtiter plates. Virus was added and culture continued for 3 days at 37°C.

HIV RNA assay:

5 Cell lysates or purified RNA in 3 M or 5 M GED were mixed with 5 M GED and capture probe to a final guanidinium isothiocyanate concentration of 3 M and a final biotin oligonucleotide concentration of 30 nM. Hybridization was carried out in sealed U bottom 96 well tissue culture plates
10 (Nunc or Costar) for 16-20 hours at 37°C. RNA hybridization reactions were diluted three-fold with deionized water to a final guanidinium isothiocyanate concentration of 1 M and aliquots (150 µL) were transferred to streptavidin coated microtiter plates wells. Binding of capture probe and
15 capture probe-RNA hybrid to the immobilized streptavidin was allowed to proceed for 2 hours at room temperature, after which the plates were washed 6 times with DuPont ELISA plate wash buffer (phosphate buffered saline(PBS), 0.05% Tween 20.) A second hybridization of reporter probe to the immobilized
20 complex of capture probe and hybridized target RNA was carried out in the washed streptavidin coated well by addition of 120 µl of a hybridization cocktail containing 4 X SSC, 0.66% Triton X 100, 6.66% deionized formamide, 1 mg/mL BSA and 5 nM reporter probe. After hybridization for one
25 hour at 37°C, the plate was again washed 6 times. Immobilized alkaline phosphatase activity was detected by addition of 100 µL of 0.2 mM 4-methylumbelliferyl phosphate (MUBP, JBL Scientific) in buffer δ (2.5 M diethanolamine pH 8.9 (JBL Scientific), 10 mM MgCl₂, 5 mM zinc acetate dihydrate
30 and 5 mM N-hydroxyethyl-ethylene-diamine-triacetic acid). The plates were incubated at 37°C. Fluorescence at 450 nM was measured using a microplate fluorometer (Dynateck) exciting at 365 nM.

35 Microplate based compound evaluation in HIV-1 infected MT-2 cells:

Compounds to be evaluated were dissolved in DMSO and diluted in culture medium to twice the highest concentration

to be tested and a maximum DMSO concentration of 2%. Further three-fold serial dilutions of the compound in culture medium were performed directly in U bottom microtiter plates (Nunc). After compound dilution, MT-2 cells (50 μ L) were added to a final concentration of 5×10^5 per mL (1×10^5 per well). Cells were incubated with compounds for 30 minutes at 37°C in a CO₂ incubator. For evaluation of antiviral potency, an appropriate dilution of HIV-1 (RF) virus stock (50 μ L) was added to culture wells containing cells and dilutions of the test compounds. The final volume in each well was 200 μ L. Eight wells per plate were left uninfected with 50 μ L of medium added in place of virus, while eight wells were infected in the absence of any antiviral compound. For evaluation of compound toxicity, parallel plates were cultured without virus infection.

After 3 days of culture at 37°C in a humidified chamber inside a CO₂ incubator, all but 25 μ L of medium/well was removed from the HIV infected plates. Thirty seven μ L of 5 M GED containing biotinylated capture probe was added to the settled cells and remaining medium in each well to a final concentration of 3 M GED and 30 nM capture probe. Hybridization of the capture probe to HIV RNA in the cell lysate was carried out in the same microplate well used for virus culture by sealing the plate with a plate sealer (Costar), and incubating for 16-20 hrs in a 37°C incubator. Distilled water was then added to each well to dilute the hybridization reaction three-fold and 150 μ L of this diluted mixture was transferred to a streptavidin coated microtiter plate. HIV RNA was quantitated as described above. A standard curve, prepared by adding known amounts of pDAB 72 in vitro RNA transcript to wells containing lysed uninfected cells, was run on each microtiter plate in order to determine the amount of viral RNA made during the infection.

In order to standardize the virus inoculum used in the evaluation of compounds for antiviral activity, dilutions of virus were selected which resulted in an IC₉₀ value (concentration of compound required to reduce the HIV RNA level by 90%) for dideoxycytidine (ddC) of 0.2 μ g/mL. IC₉₀

values of other antiviral compounds, both more and less potent than ddC, were reproducible using several stocks of HIV-1 (RF) when this procedure was followed. This concentration of virus corresponded to $\sim 3 \times 10^5$ PFU (measured by plaque assay on MT-2 cells) per assay well and typically produced approximately 75% of the maximum viral RNA level achievable at any virus inoculum. For the HIV RNA assay, IC₉₀ values were determined from the percent reduction of net signal (signal from infected cell samples minus signal from uninfected cell samples) in the RNA assay relative to the net signal from infected, untreated cells on the same culture plate (average of eight wells). Valid performance of individual infection and RNA assay tests was judged according to three criteria. It was required that the virus infection should result in an RNA assay signal equal to or greater than the signal generated from 2 ng of pDAB 72 *in vitro* RNA transcript. The IC₉₀ for ddC, determined in each assay run, should be between 0.1 and 0.3 $\mu\text{g/mL}$. Finally, the plateau level of viral RNA produced by an effective protease inhibitor should be less than 10% of the level achieved in an uninhibited infection. A compound was considered active if its IC₉₀ was found to be less than $1\mu\text{M}$.

For antiviral potency tests, all manipulations in microtiter plates, following the initial addition of 2X concentrated compound solution to a single row of wells, were performed using a Perkin Elmer/Cetus ProPette.

Dosage and Formulation

The antiviral compounds of this invention can be administered as treatment for viral infections by any means that produces contact of the active agent with the agent's site of action, i.e., the viral protease, in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but preferably are administered with a pharmaceutical carrier

selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. A daily dosage of active ingredient can be expected to be about 0.001 to about 1000 milligrams per kilogram of body weight, with the preferred dose being about 0.1 to about 30 mg/kg.

Dosage forms of compositions suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders, or in liquid dosage forms, such as elixirs, syrups and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral

administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either
5 alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts, and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben and chlorobutanol. Suitable pharmaceutical carriers are
10 described in *Remington's Pharmaceutical Sciences, supra*, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

15

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50
20 mg of cellulose, and 6 mg magnesium stearic.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared
25 and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules should then be washed and dried.

30 Tablets

A large number of tablets can be prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 mg of microcrystalline
35 cellulose, 11 mg of starch and 98.8 mg of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 25 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mg of vanillin.

Injectable

A parenteral composition suitable for administration by injection can be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is sterilized by commonly used techniques.

Combination of components (a) and (b)

Each therapeutic agent component of this invention can independently be in any dosage form, such as those described above, and can also be administered in various ways, as described above. In the following description component (b) is to be understood to represent one or more agents as described previously. Thus, if components (a) and (b) are to be treated the same or independently, each agent of component (b) may also be treated the same or independently.

Components (a) and (b) of the present invention may be formulated together, in a single dosage unit (that is, combined together in one capsule, tablet, powder, liquid, etc.) as a combination product. When component (a) and (b) are not formulated together in a single dosage unit, component (a) may be administered at the same time as component (b) or in any order; for example component (a) of this invention may be administered first, followed by administration of component (b), or they may be administered in the reverse order. If component (b) contains more than one agent, e.g., one RT inhibitor and one protease inhibitor, these agents may be administered together or in any order. When not administered at the same time, preferably the administration of component (a) and (b) occurs less than about one hour apart. Preferably, the route of

administration of component (a) and (b) is oral. The terms oral agent, oral inhibitor, oral compound, or the like, as used herein, denote compounds which may be orally administered. Although it is preferable that component (a) and component (b) both be administered by the same route (that is, for example, both orally) or dosage form, if desired, they may each be administered by different routes (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously) or dosage forms.

As is appreciated by a medical practitioner skilled in the art, the dosage of the combination therapy of the invention may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

The proper dosage of components (a) and (b) of the present invention will be readily ascertainable by a medical practitioner skilled in the art, based upon the present disclosure. By way of general guidance, typically a daily dosage may be about 100 milligrams to about 1.5 grams of each component. If component (b) represents more than one compound, then typically a daily dosage may be about 100 milligrams to about 1.5 grams of each agent of component (b). By way of general guidance, when the compounds of component (a) and component (b) are administered in combination, the dosage amount of each component may be reduced by about 70-80% relative to the usual dosage of the component when it is administered alone as a single agent for the treatment of HIV infection.

The combination products of this invention may be formulated such that, although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized. In order to minimize contact, for example, where the product is orally administered, one active ingredient may be enteric coated.

By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines.

Another embodiment of this invention where oral administration is desired provides for a combination product wherein one of the active ingredients is coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component. In each formulation wherein contact is prevented between components (a) and (b) via a coating or some other material, contact may also be prevented between the individual agents of component (b).

Dosage forms of the combination products of the present invention wherein one active ingredient is enteric coated can be in the form of tablets such that the enteric coated component and the other active ingredient are blended together and then compressed into a tablet or such that the enteric coated component is compressed into one tablet layer and the other active ingredient is compressed into an additional layer. Optionally, in order to further separate the two layers, one or more placebo layers may be present such that the placebo layer is between the layers of active

ingredients. In addition, dosage forms of the present invention can be in the form of capsules wherein one active ingredient is compressed into a tablet or in the form of a plurality of microtablets, particles, granules or non-perils, which are then enteric coated. These enteric coated microtablets, particles, granules or non-perils are then placed into a capsule or compressed into a capsule along with a granulation of the other active ingredient.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time or concurrently by the same manner, will be readily apparent to those skilled in the art, based on the present disclosure.

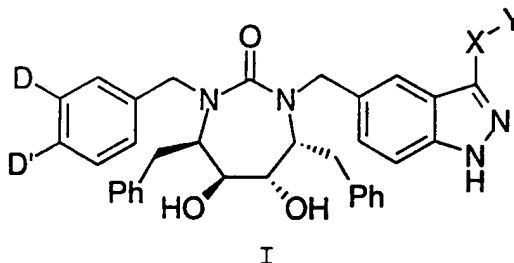
Pharmaceutical kits useful for the treatment of HIV infection, which comprise a therapeutically effective amount of a pharmaceutical composition comprising a compound of component (a) and one or more compounds of component (b), in one or more sterile containers, are also within the ambit of the present invention. Sterilization of the container may be carried out using conventional sterilization methodology well known to those skilled in the art. Component (a) and component (b) may be in the same sterile container or in separate sterile containers. The sterile containers of materials may comprise separate containers, or one or more multi-part containers, as desired. Component (a) and component (b), may be separate, or physically combined into a single dosage form or unit as described above. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as for example, one or more pharmaceutically acceptable carriers, additional vials for mixing the components, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced
5 otherwise than as specifically described herein.

WHAT IS CLAIMED AS NEW AND DESIRED TO BE SECURED BY
LETTER PATENT OF UNITED STATES IS:

1. A compound of formula I:

5



or a pharmaceutically acceptable salt thereof, wherein:

10 one of D and D' is NH₂ and the other selected from H, halogen, C₁₋₆ alkoxy, and C₁₋₆ alkyl;

X is selected from a bond, CH=CHCH₂, CH₂CH₂CH₂, CH₂CH₂, CH(OH), and CH₂;

15

Y is selected from OR¹, SR¹, NR¹R⁶, -CN, -OC(O)NR¹R², -NR³C(O)OR¹, -NR³C(O)NR¹R², -C(O)NR¹R², -NR³ac(O)R¹, -C(O)R¹, -C(O)OR¹, -C(OH)(R²)R¹, -SO₂R⁵, -SO₂NR¹R², and -(CH₂)_mR⁴;

20

R¹ is selected from H, (CH₂)_nR⁵, C₁₋₆ alkyl substituted with 0, 1, 2, or 3 R^{1a}, and C₂₋₆ alkenyl substituted with 0, 1, or 2 R^{1a};

25 R^{1a} is selected from C₁₋₆ alkoxy, OH, =O, halogen, C₃₋₆ cycloalkyl, and NR⁶R^{6a};

30 R² is selected from H, C₁₋₄ alkyl substituted with 0, 1, or 2 R^{2b}, phenyl substituted with 0, 1, or 2 R⁷, and a 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R⁷;

R^{2b} is selected from C₁₋₆ alkoxy, OH, halogen, and NR⁶R^{6a};

R³ is selected from H and CH₃;

R^{3a} is selected from H and C₁₋₃ alkyl;

5

R⁴ is selected from a 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R⁷;

10

R⁵ is selected from a C₃₋₁₀ carbocyclic residue substituted with 0, 1, or 2 R⁷, and a 5-10 membered heterocyclic system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R⁷;

15

R⁶ and R^{6a} are independently selected from H and C₁₋₄ alkyl;

R⁷ is selected from halogen, OH, =O, C₁₋₆ alkoxy, -CN, -NO₂, NR⁶R^{6a}, COR⁸, C₁₋₆ alkyl, CF₃, and S(O)_p(C₁₋₆ alkyl);

20

R⁸ is selected from H, C₁₋₆ alkyl, C₁₋₆ alkoxy, and NR⁶R^{6a};

m is 0, 1, 2, or 3;

25

n is 0, 1, or 2; and,

p is 0, 1, or 2.

30

2. A compound according to Claim 1, wherein:

D is NH₂;

35 D' is H;

X is CH₂; and,

Y is selected from OR^1 , SR^1 , NR^1R^6 , $-CN$, $-OC(O)NR^1R^2$,
 $-NR^3C(O)OR^1$, $-NR^3C(O)NR^1R^2$, $-C(O)NR^1R^2$, $-NR^3aC(O)R^1$,
 $-C(O)R^1$, $-SO_2R^5$, $-SO_2NR^1R^2$, and $-(CH_2)_mR^4$.

5

3. A compound according to Claim 2, wherein:

Y is selected from OR^1 , SR^1 , $-OC(O)NR^1R^2$, $-NR^3C(O)OR^1$,
 $-NR^3C(O)NR^1R^2$, $-C(O)NR^1R^2$, $-NR^3aC(O)R^1$, $-C(O)R^1$,
10 $-C(O)OR^1$, $-SO_2R^5$, $-SO_2NR^1R^2$, and $-(CH_2)_mR^4$.

R^1 is selected from H, $(CH_2)_nR^5$ and C_{1-6} alkyl substituted
with 0, 1, 2, or 3 R^{1a} ;

15 R^2 is selected from H, C_{1-4} alkyl substituted with 0, 1, or 2
 R^{2b} , phenyl substituted with 0, 1, or 2 R^7 , and a 5-10
membered heterocyclic system containing from 1-3
heteroatoms selected from the group consisting of N, O,
and S substituted with 0, 1, or 2 R^7 ; and,

20

R^5 is selected from a C_{6-10} aromatic carbocyclic residue
substituted with 0, 1, or 2 R^7 , and a 5-10 membered
aromatic heterocyclic system containing from 1-3
heteroatoms selected from the group consisting of N, O,
25 and S substituted with 0, 1, or 2 R^7 .

4. A compound according to Claim 3, wherein:

30 Y is selected from OR^1 , SR^1 , $-OC(O)NR^1R^2$, $-NR^3C(O)OR^1$,
 $-C(O)NR^1R^2$, $-NR^3aC(O)R^1$, $-C(O)R^1$, and $-(CH_2)_mR^4$.

R^1 is selected from $(CH_2)_nR^5$ and C_{1-6} alkyl;

35 R^4 is selected from a 5-10 membered aromatic heterocyclic
system containing from 1-3 heteroatoms selected from the
group consisting of N, O, and S substituted with 0, 1,
or 2 R^7 ;

R⁵ is selected from a C₆₋₁₀ aromatic carbocyclic residue substituted with 0, 1, or 2 R⁷, and a 5-10 membered aromatic heterocyclic system containing from 1-2
5 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R⁷;

R⁷ is selected from halogen, OH, C₁₋₆ alkoxy, -CN, -NO₂,
NR⁶R^{6a}, COR⁸, C₁₋₆ alkyl, CF₃, and S(O)₂(C₁₋₄ alkyl); and,
10 m is 0, 1, or 2.

5. A compound according to Claim 4, wherein:
15

R² is selected from H, C₁₋₄ alkyl substituted with 0, 1, or 2 R^{2b}, phenyl substituted with 0, 1, or 2 R⁷, and a 5-10 membered heterocyclic system containing from 1-2
20 heteroatoms selected from the group consisting of N, O, and S substituted with 0, 1, or 2 R⁷; and,

R⁷ is selected from Cl, F, I, OH, C₁₋₆ alkoxy, -CN, -NO₂,
NR⁶R^{6a}, COR⁸, C₁₋₆ alkyl, CF₃, and S(O)₂(C₁₋₄ alkyl); and,
25 n is 0 or 1.

6. A compound according to Claim 1, wherein:

30 D is NH₂;

D' is H;

X is CH₂; and,
35

Y is selected from:
phenylmethoxy; phenylthio; 2-benzimidazolylthio;
2-quinolinylmethoxy; 4-trifluoromethylphenoxy; 6-

quinolinoxy; 5-quinolinoxy; 4-quinolinoxy; 2-methylphenoxy; 3-fluorophenylmethoxy; 2-fluorophenylmethoxy; ethoxy; 7-quinolinoxy; 4-methylphenylmethoxy; 4-trifluoromethylphenylmethoxy; 3-methylphenoxy; 3-aminophenoxy; 2-aminophenoxy; 3-methylphenylmethoxy; 3-trifluoromethylphenylmethoxy; 5-(2-methyl)benzthiazoloxy; 5-benzthiazoloxy; n-butoxy; 4-cinnolinoxy; 4-fluoro-2-aminophenoxy; methyl carbamoyl; 4-cyano-2-methoxyphenoxy; i-butyl carbamoyl; methoxy; 1-(5-methyl)indazole; ethyl carbamoyl; N-phenyl carbamoyl; 1-pyrazole; n-propyl carbamoyl; 3,4-dimethoxyphenoxy; n-butyl carbamoyl; i-propyl carbamoyl; t-butyl carbamoyl; trifluoroacetamido; 2,2,2-trifluoroethyl carbamoyl; 3-tetrahydrofuranlyl carbamoyl; 1-(4-methyl)pyrazole; 1-(4-chloro)pyrazole; 1-(4-bromo)pyrazole; 2-pyridinyl carboxamido; phenyl carboxamido; 1-(4-amino)pyrazole; 1-(3-trifluoromethyl)pyrazole; 1-(3,5-dimethoxy)pyrazole; 1-(3-amino)pyrazole; 2-furanlyl carboxamido; 2-thiophenyl carboxamido; 1-(4-iodo)pyrazole; 1-(4-nitro)pyrazole; 1-(3-nitro)pyrazole; t-butyl carboxamido; 3-trifluoromethylphenyl carboxamido; 3-methoxyphenyl carboxamido; 4-methoxyphenyl carboxamido; 2-quinolinyl carboxamido; 2-pyrazinyl carboxamido; 1-i-quinolinyl carboxamido; 2-methoxyphenyl carboxamido; 1-(4-carboethoxy)pyrazole; 2-fluorophenyl carboxamido; 3-fluoro-5-trifluoromethylphenoxy; 4-fluorophenyl carboxamido; 8-(1,2,3,4-tetrahydro)quinolinyl carboxamido; 2-(6-methyl)pyridinyl carboxamido; 2-aminophenyl carboxamido; 3-aminophenyl carboxamido; 4-aminophenyl carboxamido; 2,6-difluorophenyl carboxamido; 1-(4-acetyl)pyrazole; 1-(4-carbomethoxy)pyrazole; 2-pyridylmethoxy; 2-methyl-4-thiazolemethoxy; propoxy; N,N-dimethylcarbamoyl; 6-methyl-2-pyridylmethoxy; phenoxy; 2-isopropyl-4-thiazolemethoxy; 4-methylphenoxy; 4-methoxyphenoxy; 4-cyanophenoxy; 3-pyridoxy; 2-methyl-6-benzothiazoloxy; 5-trifluoromethyl-2-pyridylmethoxy; N-methylcarbamoyl; N-isopropylcarbamoyl; 2-methyl-5-pyridoxy; 1,2,4-triazole; benzoyl; N-t-butylcarboxamido;

N,N-diethylcarboxamido; N-phenylcarboxamido;
pyrrolidinecarboxamido; 4-fluorophenoxy; 3-
fluorophenoxy; 4-fluorophenylmethoxy; 2-naphthylmethoxy;
2-naphthoxy; 2-fluorophenoxy; 4-chlorophenoxy;
5 2,4-di-fluorophenoxy; 4-(methylsulfonyl)phenoxy; 2-
fluoro-3-pyridoxy; 2-benzothiazolemethoxy; 3-
cyanophenoxy; 3,4-di-fluorophenoxy; 2-fluoro-4-
pyridylmethoxy; 6-fluoro-2-pyridylmethoxy; 5-chloro-3-
pyridoxy; 3-chloro-6-pyridazoxy; 8-quinolinoxy; 6-
10 chloro-2-pyridylmethoxy; 2-chloro-3-pyridoxy; 3-methoxy-
phenoxy; 2-methoxy-phenoxy; 3-furanoxy; 3-acetylphenoxy;
2-thiazole; 2-benzimidazole; N-methyl-2-imidazole; 4-
acetyl phenoxy; 6-cyano-2-pyridyl; 2-pyridazole; 2-
benzothiazole; phenylmethyl; 2-pyridyl; 2-isoxazole;
15 2-furan;

7. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and a therapeutically
20 effective amount of a compound of one of Claims 1-6 or a
pharmaceutically acceptable salt form thereof.

8. A method for treating HIV infection which comprises
25 administering to a host in need of such treatment a
therapeutically effective amount of a compound of one of
Claims 1-6 or a pharmaceutically acceptable salt form
thereof.

30 9. A method of treating HIV infection which comprises
administering, in combination, to a host in need thereof a
therapeutically effective amount of:

- (a) a compound of one of Claims 1-6; and,
35 (b) at least one compound selected from the group
consisting of HIV reverse transcriptase inhibitors and HIV
protease inhibitors.

10. A method according to Claim 9, wherein the reverse transcriptase inhibitor is a nucleoside reverse transcriptase inhibitor.

5

11. A method according to Claim 10, wherein the nucleoside reverse transcriptase inhibitor is selected from AZT, 3TC, ddI, ddC, and d4T and the protease inhibitor is
10 selected from saquinavir, ritonavir, indinavir, VX-478, nelfinavir, KNI-272, CGP-61755, and U-103017.

12. A method according to Claim 11, wherein the
15 nucleoside reverse transcriptase inhibitor is selected from AZT and 3TC and the protease inhibitor is selected from saquinavir, ritonavir, and indinavir.

20 13. A method according to Claim 12, wherein the nucleoside reverse transcriptase inhibitor is AZT.

25 14. A method according to Claim 12, wherein the protease inhibitor is indinavir.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 98/05901

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D403/06 A61K31/55 C07D403/14 C07D401/06 C07D417/14
C07D405/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 532 356 A (SMYSER T E ET AL) 2 July 1996 R31 can be indazoly]. see column 22; claim 1 ---	1-7
X	US 5 610 294 A (LAM P Y ET AL) 11 March 1997 cited in the application R31 can be indazole see column 21, line 8; claim 1 --- -/--	1-7

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 July 1998

Date of mailing of the international search report

20/08/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/05901

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	<p>WILKERSON W W ET AL: "Nonsymmetrically Substituted Cyclic Urea HIV Protease Inhibitors" J. MED. CHEM. (JMCMAR,00222623);97; VOL.40 (25); PP.4079-4088, DUPONT MERCK PHARMACEUTICAL COMPANY;WILMINGTON; 19880-0500; DE; USA (US), XP002071101 see tables 1,2</p> <p style="text-align: center;">----</p>	1-7
P,A	<p>RODGERS J D ET AL: "Potent cyclic urea HIV protease inhibitors with benzofused heterocycles as P2/P2' groups" BIOORG. MED. CHEM. LETT. (BMCLE8,0960894X);96; VOL.6 (24); PP.2919-2924, DUPONT MERCK PHARMACEUTICAL COMPANY;WILMINGTON; 19880-0500; DE; USA (US), XP002071102 see the whole document</p> <p style="text-align: center;">----</p>	1-7
P,A	<p>US 5 683 999 A (JADHAV P K ET AL) 4 November 1997 see claim 1</p> <p style="text-align: center;">----</p>	1-7
E	<p>WO 98 20009 A (DU PONT MERCK PHARMA) 14 May 1998 see claim 1; example I</p> <p style="text-align: center;">----</p>	1-7
E	<p>WO 98 20008 A (DU PONT MERCK PHARMA) 14 May 1998 Compound (I) see claim 1</p> <p style="text-align: center;">----</p>	1-7
A	<p>JADHAV P K ET AL: "Cyclic Urea Amides: HIV-1 Protease Inhibitors with Low Nanomolar Potency against both Wild Type and Protease Inhibitor Resistant Mutants of HIV" J. MED. CHEM. (JMCMAR,00222623);97; VOL.40 (2); PP.181-191, DUPONT MERCK PHARMACEUTICAL COMPANY;DUPONT MERCK RESEARCH LABORATORIES; WILMINGTON; 19880; DE; USA (US), XP002071103 see the whole document</p> <p style="text-align: center;">-----</p>	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/05901

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5532356	A 02-07-1996	AU 5975296 A EP 0830349 A WO 9639393 A	24-12-1996 25-03-1998 12-12-1996
US 5610294	A 11-03-1997	AU 3289595 A AU 6549394 A EP 0686151 A JP 8509700 T WO 9419329 A US 5559252 A US 5506355 A CA 2156594 A ZA 9401325 A AT 156123 T AU 2871592 A AU 6180894 A BR 9206623 A CA 2120925 A CZ 9400814 A DE 69221309 D DE 69221309 T DK 607334 T EP 0607334 A EP 0765873 A ES 2104946 T FI 941649 A HU 67285 A JP 7500324 T NO 941278 A SK 40794 A WO 9307128 A LV 10096 A,B	23-05-1996 14-09-1994 13-12-1995 15-10-1996 01-09-1994 24-09-1996 09-04-1996 01-09-1994 25-08-1995 15-08-1997 03-05-1993 07-07-1994 02-05-1995 15-04-1993 16-11-1994 04-09-1997 11-12-1997 16-02-1998 27-07-1994 02-04-1997 16-10-1997 31-05-1994 28-03-1995 12-01-1995 10-06-1994 07-12-1994 15-04-1993 10-05-1994
US 5683999	A 04-11-1997	AU 5310096 A CA 2215536 A EP 0815108 A WO 9629329 A	08-10-1996 26-09-1996 07-01-1998 26-09-1996
WO 9820009	A 14-05-1998	NONE	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/05901

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9820008	A	14-05-1998 ^a	NONE

Form PCT/ISA/210 (patent family annex) (July 1992)